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THE NATURAL HISTORY OF THE PIGMENTED NEVUS; FACTORS OF AGE AND ANATOMIC LOCATION*

HERBERT Z. LUND, M.D., and GODFREY DORR STOBBE, M.D.

(From the Institute of Pathology of Western Reserve University and University Hospitals of Cleveland, Cleveland, Ohio)

The pigmented nevus undergoes a peculiar pattern of development and structural differentiation throughout life. This was first described by Unna[1,2] and little has been added to his original observations. Although different types of pigmented nevi are distinguished, many actually represent the same process in different phases of development.

Recently, stress has been laid on the "junctional" or "dermo-epidermal" nevus, in which there is proliferation of cells in the epidermis and at the dermo-epidermal junction. Traub and Keil,[3] in agreement with Kaufmann-Wolf,[4] regard this proliferation as "potentially malignant (precancerous)" whether it arises early or late in life. To Allen[5] it is the "most precarious of the precancerous lesions" of the skin. Allen,[6] however, points out that this special significance is to be attached only after puberty. Sachs, MacKee, Schwartz, and Pierson[7] distinguish the junctional nevus from the "intradermic nevus" or common mole, and consider it to be the only forerunner of nevocarcinoma. Miescher[8] does not agree with Kaufmann-Wolf that proliferation of cells at the junctional zone is in itself evidence of malignant neoplasia. He regards it as part of "nevogenesis" and precancerous only in the sense that the primary lesion of melanoblastoma† is an alteration of this form of proliferation. Some of these authors present objective evidence in support of their views, but more is needed.

The full significance of the histologic features of nevi and melanoblastoma can be learned only after certain data are gathered and cor-

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† Throughout this paper the term melanoblastoma designates the malignant neoplasm for which nevocarcinoma, malignant melanoma, and malignant melanoblastoma are considered by some to be acceptable synonyms.—*Editor.*

relations made. First, the usual appearances and extent of variation of ordinary nevi of patients of all ages and in all anatomic sites are to be determined. Second, comparisons are to be made with proved melanoblastomas. Third, it remains to be determined that histologic evaluation affords reliable information as to the eventual outcome. This investigation undertakes the first of these steps.

The older literature on the histologic appearance of nevi in different age groups and the origin of the nevus cell has been well covered by Fox,[9] Fick,[10] Frédéric,[11] Gans,[12] and Riecke.[13] Theories of epithelial, endothelial, connective tissue, and neural origin were proposed. The more systematic analyses of developmental changes throughout life were by Unna[1,2] and other supporters of the theory of epithelial origin of nevus cells.

In presenting his arguments for the neural nature of nevus cells, Masson[14] again pointed out differences between incipient and old nevi. However, his work and that of Feyrter[15] and of John[16] have been concerned largely with cytologic detail, and comparatively few nevi were reported. Among his 10 cases, Feyrter described a nevus of a patient 1 year old. The remainder were in adults. John based most of his impressions of the appearance of young nevi on a case of leukoderma acquisitum centrifugum of short duration, although the patient was an adult. In his other cases the age varied. The youngest age specifically stated was 12 years. The larger series of Miescher and von Albertini[17] and of Montgomery and Kernohan[18] included nevi of subjects of various ages, but no correlation was made between the appearance of the nevi and the age of the patients. The recent article of Spitz[19] contributes valuable information concerning the nevi of childhood but does not pretend to be an inclusive decade-by-decade analysis.

Method and Results

Two hundred nevi, considered to be benign both clinically and histologically, were studied. Representation of various ages and locations was sought for, but otherwise the selection was random. When multiple nevi were excised from one patient, each was considered separately. Blue nevi were omitted.

About ten lesions previously designated as pigmented nevi were reclassified as lentigines. They were from patients of all age groups and, although the distinction of lentigo from nevus is not clear, they were not included in the series. They consisted of hyperpigmented epidermis with occasional clear cells scattered along the deeper zone. There were

no well defined intra-epidermal clumps and no nevus cells in the corium. Occasional melanophores were present, however.

The nevi were subdivided as to the age of the patient and as to the following regions: (1) head and neck, exclusive of conjunctiva; (2) trunk, including external genitalia and perineum; (3) shoulders, arms, buttocks, and thighs (designated as the proximal parts of the extremities); (4) forearms, hands, legs, and feet (designated as the distal parts of the extremities).

Routine surgical material was used. Descriptions and opinions are therefore based on the appearance of one or a few planes of section. While serial sections might disclose certain details, as for example sparse foci of junctional proliferation, the method pursued is adequate for comparisons and for the establishment of a trend in a series as large as this.

Clinical records were examined and as many cases as possible were followed for different periods of time. Histories concerning nevi are usually inadequate and some of the moles were removed incidental to other surgical procedures. Data based on the patient's ideas of duration were obtained in 87.5 per cent of cases, concerning growth of nevi in 87.5 per cent, and follow-up from the time of the surgical excision to the time of the analysis was successful in 88.5 per cent.

In 89.7 per cent of cases in which there was information, the nevus was said to have been present from birth or childhood, or in adults for an indefinitely long time. Therefore, the trends presented in the following discussion are to be correlated not only with the age of the patient but also approximately with the duration of the nevus. The exceptions are analyzed in a later section.

Of the 177 cases with follow-up, there was recurrence in 3 cases but there was no subsequent growth nor was there histologic evidence of melanoblastoma. Nine patients died subsequently, one of carcinoma of the stomach, 2 of carcinoma of the breast, one of heart disease, one of pemphigus, one of alcoholism, one was killed in action in World War II, and for 2 the cause of death was unstated. Follow-up was carried out on one case for 1 month, 2 for 5 months, 2 for 6 months, 28 for 1 year, 18 for 2 years, 8 for 3 years, 20 for 4 years, 60 for 5 to 9 years, 23 for 10 to 14 years, and 15 for 15 to 19 years.

Special attention was directed toward size and shape of the nevi, junctional and intra-epidermal cellular proliferation, mitotic figures, distribution of nevus cells, presence of fibrillar and nerve-like elements, pigmentation, multinucleated cells, inflammation, vascular changes, and

miscellaneous observations. Correlation with certain clinical features was made.

Size and General Configuration. The nevi were segregated as narrow stratified, broad stratified, and bulky according to the general unmagnified view of the microscopic section. By "narrow stratified" is meant a slender zone of cells in the epidermis or corium lying parallel to the skin surface. Approximately 0.6 mm. was considered the critical width between narrow and broad. By "broad stratified" is meant a similar zone of cells exceeding 0.6 mm. but not exceeding a width of about 2.0 mm. By "bulky" is meant still broader stratified nevi and large nevi of nodular and irregular shapes. The tabulation of results by age and anatomic location is shown in Table I.

It is evident that there are certain relationships between both age and location and the size and shape of nevi. The narrow stratified nevi are

TABLE I

Size and General Configuration of Nevi According to Age and Anatomic Site

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and Neck								
Narrow stratified	2	2	0	0	0	0	1	5
Broad stratified	5	2	1	0	2	0	0	10
Bulky	2	6	7	8	6	11	8	48
Trunk								
Narrow stratified	7	2	0	1	1	3	0	14
Broad stratified	1	2	2	0	0	1	2	8
Bulky	2	8	9	6	9	5	6	45
Extremities, proximal								
Narrow stratified	1	0	0	0	0	0	0	1
Broad stratified	1	1	0	0	1	3	0	6
Bulky	0	3	6	4	8	2	1	24
Extremities, distal								
Narrow stratified	5	4	2	5	4	1	0	21
Broad stratified	2	1	3	1	2	0	0	9
Bulky	2	1	2	0	1	3	0	9
Totals								
Narrow stratified	15	8	2	6	5	4	1	41
Broad stratified	9	6	6	1	5	4	2	33
Bulky	6	18	24	18	24	21	15	126
	30	32	32	25	34	29	18	200

most common in the first decade. The proportion of bulky nevi is greater in the second decade and still greater in the third, but thereafter there is little change. This roughly indicates the rate of growth or cellular multiplication of nevi. At all ages the narrow stratified nevi are least common on the head and neck, and most common on the distal parts of the extremities.

Junctional and Intra-epidermal Cellular Proliferation. The cells of a pigmented nevus vary in appearance in the epidermis and corium. By "nevus cell" is meant the characteristic cell of the corium. It is described subsequently. The cells of the epidermis and junctional zone are often designated as the "clear cells." The term is not entirely descriptive because the density, amount, and degree of pigmentation of the cytoplasm vary. Furthermore, there is no clear-cut distinction from nevus cells, for transitions in appearance and direct continuity with nevus cells can be seen. In this paper these cells are spoken of as the intra-epidermal cells or junctional cells of the nevus.

The junctional cells usually appear in round clumps within the epidermis or attached to the deep surface of the epidermis. Clumps of cells separated from the epidermis by collagenous fibrils ("snared off") are designated as subjunctional. Undoubtedly some of the clumps so designated could be demonstrated to connect with the epidermis if serial sections were made. However, for the purposes of comparison and charting it was decided that the term junctional proliferation should be restricted to the cells within the epidermis or joined to it at its deep margin.

Infrequently there is blending of broad bands of cells in the superficial corium with those of the epidermis. These cells are not in clumps and often resemble the deeper nevus cells more closely than the intra-epidermal "clear" cells. This appearance was called junctional proliferation also. However, it is almost invariably associated with the usual type of junctional proliferation and its inclusion does not significantly affect the tabulation.

It was apparent from the start that junctional proliferation is a quantitative consideration. The proliferation was classified as marked, moderate, slight, or none. "Marked" means many foci of proliferation; "moderate," occasional; "slight," sparse; "none," that no such change was found, or, at most, a rare focus of proliferation of a few intra-epidermal cells or junction of a few cells in the epidermis and dermis. In some instances isolated "clear" cells were present in the basal layer of the epidermis. Rarely a few were grouped together. This is often associated with hyperpigmentation of the basal layer, and is not classified as junctional proliferation, because there is no proliferation of clumps or extension of such cells downward from the epidermis. These changes are the same as in lentigo.

The observations of junctional proliferation are applied to hair follicles as well as to the surface epithelium. Proliferation of cells in sweat glands is evident only in the nevi of the first decade. The fact that nevi

in this decade are comparatively acellular permits easy distinction of these foci. However, it is reasonably certain that the diminution in subsequent decades is absolute. The observations are recorded in relation to age and location in Table II and in relation to size and shape of

TABLE II

Junctional Proliferation According to Age and Site

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and Neck								
Marked	3	0	0	0	0	0	0	3
Moderate	4	2	0	0	0	1	0	7
Slight	1	3	0	1	0	0	0	5
None	1	5	8	7	8	10	9	48
Trunk								
Marked	5	2	0	0	0	0	0	7
Moderate	4	3	2	0	0	1	0	10
Slight	0	5	3	3	0	1	0	12
None	1	2	6	4	10	7	8	38
Extremities, proximal								
Marked	2	0	0	0	0	0	0	2
Moderate	0	3	1	0	0	0	0	4
Slight	0	1	1	1	0	0	0	3
None	0	0	4	3	9	5	1	22
Extremities, distal								
Marked	8	3	3	3	1	0	0	18
Moderate	1	1	0	2	1	0	0	5
Slight	0	1	1	0	3	1	0	6
None	0	1	3	1	2	3	0	10
Totals								
Marked	18	5	3	3	1	0	0	30
Moderate	9	9	3	2	1	2	0	26
Slight	1	10	5	5	3	2	0	26
None	2	8	21	15	29	25	18	118
	30	32	32	25	34	29	18	200

nevi in Table III. The classification of size and shape is the same as that used in Table I. These tables indicate that there is significant relationship of junctional proliferation with age. The proliferation is most frequent and greatest in the first decade and rapidly diminishes in subsequent age groups.

Because of differences, it is convenient to compare the trends of the nevi of the distal parts of the extremities with those of all other locations, as shown in Table IV. Junctional proliferation in nevi of adults is more frequent when the nevi are located on the distal parts of the extremities. In this site, nonetheless, there is a diminution in degree and frequency with age, and of the 11 nevi so located in patients beyond 40 years of age, only 2 showed it to a moderate or marked degree.

There is no abrupt cessation of junctional proliferation at any age. In Table IV, the first 2 decades are subdivided into 5-year periods. This shows that the diminution in frequency begins before puberty and does not stop abruptly.

TABLE III

Junctional Proliferation According to Age and General Appearance of Nevus

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Narrow stratified nevus								
Marked	11	5	2	3	0	0	0	21
Moderate	4	1	0	1	1	1	0	8
Slight	0	0	0	0	3	0	0	3
None	0	2	0	2	1	3	1	9
Broad stratified nevus								
Marked	4	0	0	0	1	0	0	5
Moderate	3	0	1	1	0	0	0	5
Slight	1	4	1	0	0	0	0	6
None	1	2	4	0	4	4	2	17
Bulky nevus								
Marked	3	0	1	0	0	0	0	4
Moderate	2	8	2	0	0	1	0	13
Slight	0	6	4	5	0	2	0	17
None	1	4	17	13	24	18	15	92
Totals								
Marked	18	5	3	3	1	0	0	30
Moderate	9	9	3	2	1	2	0	26
Slight	1	10	5	5	3	2	0	26
None	2	8	21	15	29	25	18	118
	30	32	32	25	34	29	18	200

Although the nevi of childhood are of the narrow stratified type, it is seen from Table III that junctional proliferation is not confined to this type. Clumps of intra-epidermal cells are often found in bulky nevi.

TABLE IV

Comparison of Junctional Proliferation of Nevi of the Distal Parts of the Extremities with Nevi of All Other Sites

	Age group (*years*)								
	0–4	5–9	10–14	15–19	20–29	30–39	40–49	50–59	60–
Distal parts of the extremities	100	100	67	No cases	43	83	29	0	No cases
All other sites	86	86	60	25	12	0	0	8	0

The figures express per cent of nevi showing moderate to marked junctional proliferation.

Contrariwise, the presence of a narrow stratified nevus does not necessarily indicate a nevus of childhood or a nevus with junctional proliferation. Some nevi never do become bulky but nevertheless follow the same trend of diminished junctional proliferation with advancing years.

The exceptions to the trend are discussed later. These include the nevi

of adults which have scanty nevus cells but much junctional proliferation and thereby resemble the nevi of childhood, and the infrequent cases in which nevi of childhood lack junctional proliferation.

Mitotic Figures. Mitotic figures are rare in pigmented nevi. Miescher[8] commented that they are exceptionally infrequent in the intra-epidermal nests and may be entirely absent. The rarity was borne out by the present investigation.

In sections from the entire series, mitotic figures were identified in only 13 nevi. In 2, there were 2 mitotic figures in each. In 1, there were 5 mitotic figures. Six of the patients were in the first decade of life, 4 in the second, 2 in the third, and 1 in the fifth. In 7 cases there was moderate or marked proliferation in the epidermis or at the dermo-epidermal junction; in 2 there was slight, and in 4 no proliferation. Of the 19 mitotic figures, 5 occurred in the intra-epidermal, junctional, or immediately subjunctional cells. The remainder were in the nevus cells. They were not seen in nevus cells of the fusiform and fibrillar type. Exceptional note is made of a small nevus, said to be of over 10 years' duration, from the dorsum of the hand of a 42-year-old man. It lacked junctional cells and pigmented cells. Five mitotic figures were counted, scattered at random among the nevus cells. There has been no recurrence of this lesion 10 years after removal.

Distribution of Nevus Cells. In all cases there were nevus cells in the upper part of the corium. There was a tendency for the cells of nevi of the trunk to be closer to the epidermis than the cells of nevi of the head and neck, which tended to have a definite (although thin and focally interrupted) zone of collagenous connective tissue just beneath the epidermis.

The number of nevi with cells in the mid-corium and deep corium are shown in Table V, correlated with age and site. The nevi were classified as to the presence of none, few, or many nevus cells in the corium deep to the uppermost two or three bands of coarse collagenous tissue. This is the collagenous stratum which can be traced laterally to the adjacent normal corium, and not the finer fibrils intermingled with nevus cells.

Nevus cells were present in the deep parts of the corium in about the same proportion of nevi in all age groups. However, it is true that in older life the mass of the deep cells was greater than in the first decade as was also the mass of the superficial cells. This has not been analyzed statistically but was readily apparent in the histologic material. The largest proportion of nevi with deeply situated cells were of the head and neck. Nevi of the proximal part of the extremities, trunk, and distal part

of the extremities showed a progressively smaller proportion in the order stated.

The nevi with cells deep in the corium were further analyzed as to their relationship to hair follicles and sweat glands. Observations con-

TABLE V

Nevi Showing Cells in Deeper Part of Corium

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and neck								
None	0	0	0	0	1	0	0	1
Few	2	2	1	1	1	0	2	9
Many	7	7	7	7	6	8	6	48
Inadequate biopsy	0	1	0	0	0	3	1	5
Trunk								
None	3	4	0	3	1	3	3	17
Few	3	2	8	1	6	4	3	27
Many	3	6	3	1	2	2	0	17
Inadequate biopsy	1	0	0	2	1	0	2	6
Extremities, proximal								
None	0	0	0	0	0	2	0	2
Few	1	3	6	2	3	1	1	17
Many	1	1	0	2	6	2	0	12
Inadequate biopsy	0	0	0	0	0	0	0	0
Extremities, distal								
None	1	4	1	4	3	2	0	15
Few	4	0	3	1	3	1	0	12
Many	3	2	3	1	1	1	0	11
Inadequate biopsy	1	0	0	0	0	0	0	1
Totals								
None	4	8	1	7	5	7	3	35
Few	10	7	18	5	13	6	6	65
Many	14	16	13	11	15	13	6	88
Inadequate biopsy	2	1	0	2	1	3	3	12
	30	32	32	25	34	29	18	200

cerning this were noted by Unna,[1,2] Masson,[14] and others. The deep nevus cells were classified as: perifollicular, if all the cells formed a distinct aggregation about hair follicles and sweat glands; perifollicular and scattered, if aggregates about follicles and sweat glands were accompanied by a more diffuse distribution; scattered, if there was no distinct grouping. The results are presented in Table VI which shows that in a majority of nevi the deep cells tend to have a perifollicular pattern. Even if some of the cells appear diffusely scattered between follicles there is usually a perceptible aggregation about these structures. The perifollicular arrangement is most striking in the nevi of children, in which case the mass of cells is not bulky. It is least conspicuous in the nevi of the head and neck, especially in adult life, and is progressively

more noticeable in the proximal parts of the extremities, the trunk, and the distal parts of the extremities. The paradoxical lack of distinct perifollicular grouping in nevi of the head and neck in adults is difficult to explain but it may be related to the profusion of follicles and sweat glands causing a confluence of aggregates.

TABLE VI

Distribution of the Cells in the Deep Corium

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and Neck								
Perifollicular	3	2	0	0	0	0	0	5
Scattered	4	4	7	3	4	5	5	32
Perifollicular and scattered	2	3	1	5	3	3	3	20
Inadequate biopsy	0	1	0	0	0	3	1	5
Trunk								
Perifollicular	3	1	6	1	3	3	1	18
Scattered	1	3	2	1	3	0	2	12
Perifollicular and scattered	2	4	3	0	2	3	0	14
Inadequate biopsy	1	0	0	2	1	0	2	6
Extremities, proximal								
Perifollicular	1	3	4	1	1	1	1	12
Scattered	0	0	0	1	3	1	0	5
Perifollicular and scattered	1	1	2	2	5	1	0	12
Inadequate biopsy	0	0	0	0	0	0	0	0
Extremities, distal								
Perifollicular	5	0	5	1	2	0	0	13
Scattered	1	0	0	0	2	1	0	4
Perifollicular and scattered	1	2	1	1	0	1	0	6
Inadequate biopsy	1	0	0	0	0	0	0	1
Totals								
Perifollicular	12	6	15	3	6	4	2	48
Scattered	6	7	9	5	12	7	7	53
Perifollicular and scattered	6	10	7	8	10	8	3	52
Inadequate biopsy	2	1	0	2	1	3	3	12
	26	24	31	18	29	22	15	165

In general, deep nevus cells are found among and around the follicular epithelial cells and among and around the cells of sweat glands. This in itself does not prove an epithelial origin, for nerve fibrils and terminations are also abundant in these distributions.

Occasionally there are nevus cells among the fibers of the arrectores pilorum muscles. This may appear to refute the epithelial theory of origin but this in turn is not conclusive for the muscle is intimately related with the follicle anatomically and embryologically.

Enclosure of small vascular channels and small nerves occurs especially in the large nevi of adult life. It is not constant in random sections and does not in itself substantiate a theory of either perivascular or perineural origin of nevus cells.

Nevus cells occasionally extend as deeply as the subcutaneous fat. Infiltration among fat cells is most frequent in nevi of the head. In nevi which overlie skeletal muscle, as in those of the lip or eyelid, penetration to and around some of the superficial skeletal muscle fibers may take place. This is not to be interpreted as invasion (Fig. 8).

In summary, the superficial cells of a nevus proliferate in a zone lying parallel to the surface and in their growth tend to separate the coarsely fibrous part of the corium from the epidermis. The deep cells of a nevus tend to be distributed in and about follicles and sweat glands, although diffusely scattered cells are seen also.

Fibrillar and Nerve-like Elements. There are transitional appearances between the intra-epidermal "clear" cells and the nevus cells of the corium. The latter in turn undergo progressive changes. In the more superficial corium, especially in nevi of youth, the nevus cells may be exactly the same as the cells at the dermo-epidermal junction. A little more deeply the cells are usually somewhat smaller, usually pigment-free, but retain a large nucleus and nucleolus. Still more deeply, as a rule, the cells are smaller, nuclei are more compact, and pigment is almost always absent. Cells with nucleoli are not so abundant here as in the superficial corium. Occasionally a central pale round spot is seen in the nucleus, larger than a nucleolus and occasionally having a faint brown color. The nevus cells may be spread in large masses, or in groups surrounded by fibrils. There is gradual transition to cells of oval or fusiform type. Definition of cytoplasmic borders is lost and nuclei are adjacent to or enclosed by faintly eosinophilic fibrils, which usually run in the same axis as that of the nucleus and are sometimes arranged as ribbon-like fasciculi. These are usually seen in the lowermost part of the mass of nevus cells but may be both deep and superficial, especially in the nevi of older people. In some the fibrils are abundant and compact and often have a resemblance to Wagner-Meissner corpuscles. In the more fibrillar nevi nuclei are in many instances irregular in shape, densely stained, and often clumped. In the fibrillar parts of a nevus there are comparatively few nuclei. It is not possible to state from this study how much of this is relative, in view of the great increase of fibrils, but an absolute decrease is favored.

That the above transition in the appearance of nevus cells is developmental is shown by correlation of fibrillar elements with age. The presence of fibrils is quantitative. The degree of occurrence was classified as absent or slight, moderate, and marked. The degrees are arbitrary and difficult to define. By absent or slight is meant that none or only a few cells were associated with fibrils. By marked is meant that extensive

areas in the microscopic section were made up of fibrillar cells. Often the areas were comparatively anuclear, composed almost entirely of fibrils alone. Moderate is an intermediate appearance; the fibrillar cells were not predominant nor did they occupy large foci. The results are shown in Table VII.

TABLE VII

The Presence of Fibrillar Elements in Nevi

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and Neck								
None or few	4	4	0	1	0	0	0	9
Moderate number	2	5	4	2	1	0	0	14
Many	3	1	4	5	7	11	9	40
Trunk								
None or few	9	2	2	1	0	1	0	15
Moderate number	1	5	4	0	3	3	1	17
Many	0	5	5	6	7	5	6	34
Inadequate biopsy	0	0	0	0	0	0	1	1
Extremities, proximal								
None or few	1	1	0	0	0	0	0	2
Moderate number	1	2	2	1	1	1	1	9
Many	0	1	4	3	8	4	0	20
Extremities, distal								
None or few	5	4	3	4	2	0	0	18
Moderate number	4	1	3	1	3	1	0	13
Many	0	1	1	1	2	3	0	8
Totals								
None or few	19	11	5	6	2	1	0	44
Moderate number	8	13	13	4	8	5	2	53
Many	3	8	14	15	24	23	15	102
Inadequate biopsy	0	0	0	0	0	0	1	1
	30	32	32	25	34	29	18	200

A further segregation of nevi was made in which the nevi with foci which resembled neurofibrillar tissue were selected. Here again, criteria of selection cannot be sharply defined. It is based on the presence of readily recognized foci of delicate fibrillar tissue. Usually this is arranged in delineated ribbons and nests. In many, there are structures resembling Wagner-Meissner corpuscles. Thus the cylindroid, ribbon-like, and plate-like structures described by Masson[14] are all included. The results are shown in Table VIII.

It is evident that there is a progressive increase of fibrils and what resembles neurofibrillar tissue with increasing age, and that such tissue is the final phase of differentiation of the nevus cells. Broders and Fletcher,[20] in the interpretation of a nevus which had undifferentiated cells superficially and resembled neurofibrillar tissue deeply, came to

the same conclusion. Interpretation of the fibrillar tissue or structures resembling tactile corpuscles as the source of the nevus cells is not justifiable.

It is thought, in agreement with the interpretations of others, notably

TABLE VIII

The Presence of Nerve-like Elements

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and neck								
None	9	10	8	5	4	3	2	41
Present	0	0	0	3	4	8	7	22
Trunk								
None	10	12	9	5	6	8	4	54
Present	0	0	2	2	4	1	2	11
Inadequate biopsy	0	0	0	0	0	0	2	2
Extremities, proximal								
None	6	3	6	4	7	2	1	29
Present	0	1	0	0	2	3	0	6
Extremities, distal								
None	5	6	6	6	7	2	0	32
Present	0	0	1	0	0	2	0	3
Totals								
None	30	31	29	20	24	15	7	156
Present	0	1	3	5	10	14	9	42
Inadequate biopsy	0	0	0	0	0	0	2	2
	30	32	32	25	34	29	18	200

Kromayer[21] and Masson,[14] that the fibrils arise from the nevus cells and are not a reactive fibrosis.

In general, nevi in which fibrils are abundant are not associated with much junctional proliferation, but there are exceptions; for example, the instance recorded in the second decade (actually 12 years of age) and one instance in the third decade. In one nevus in a 7-months-old child, located on the back and not part of this series of 200, there was marked junctional proliferation but the major part of the nevus, extending from the upper cutis into the subcutaneous fat, consisted of fibrillar cells.

Pigmentation. The degree of pigmentation was arbitrarily and roughly expressed as none, 1 plus, 2 plus, 3 plus, and 4 plus. Pigmentation of the basal epidermis was not included even though it was intense in some instances and resembled the changes of lentigo. On the other hand, pigment in chromatophores among the nevus cells was included. The results in Table IX show the trend as to age and anatomic site. This

indicates that pigmentation tends to diminish with age. Furthermore, it tends to be least intense in nevi of the head and neck. The latter observation may be correlated with the additional observation that pigment is largely related to nevus cells lying in a stratum just beneath the epidermis and is not common in nevus cells around the follicles and

TABLE IX

Pigmentation According to Age and Site

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and neck								
None	1	0	0	3	2	4	3	13
One plus	3	4	5	5	3	4	3	27
Two plus	2	6	2	0	3	2	0	15
Three plus	1	0	1	0	0	0	0	2
Four plus	2	0	0	0	0	1	3	6
Trunk								
None	0	0	0	1	3	1	3	8
One plus	1	1	3	3	5	5	4	22
Two plus	4	6	4	1	2	3	1	21
Three plus	4	3	4	2	0	0	0	13
Four plus	1	2	0	0	0	0	0	3
Extremities, proximal								
None	0	0	0	1	2	3	1	7
One plus	0	0	2	2	3	1	0	8
Two plus	0	2	4	1	4	0	0	11
Three plus	2	0	0	0	0	1	0	3
Four plus	0	2	0	0	0	0	0	2
Extremities, distal								
None	0	0	0	1	1	1	0	3
One plus	1	1	3	2	1	1	0	9
Two plus	0	2	3	2	1	2	0	10
Three plus	7	3	1	1	4	0	0	16
Four plus	1	0	0	0	0	0	0	1
Totals								
None	1	0	0	6	8	9	7	31
One plus	5	6	13	12	12	11	7	66
Two plus	6	16	13	4	10	7	1	57
Three plus	14	6	6	3	4	1	0	34
Four plus	4	4	0	0	0	1	3	12
	30	32	32	25	34	29	18	200

sweat glands or diffusely scattered in the deeper corium. Even in the nevi of childhood in which intra-epidermal clumps of "clear" cells are seen along follicles and sweat glands, pigment is scanty or absent in these locations. The nevi of the face and neck, as previously noted, contain relatively more of the deeply placed diffuse and perifollicular cells.

The age distribution of pigmentation suggests a relationship to junctional proliferation, and this is borne out in the correlation of pigmentation and junctional proliferation, as shown in Table X.

The cells at the dermo-epidermal junction and of the upper part of the corium tend to be the most intensely pigmented and hence there is a rough correlation with proliferation at the dermo-epidermal junction. As pointed out, the junctional and subjunctional cells are scanty or absent in older age groups. The presence of chromatophores, usually in

TABLE X

Relationship of Pigmentation and Junctional Proliferation

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
No junctional proliferation								
No pigment	0	0	0	6	8	9	7	30
One plus	2	4	11	7	11	11	7	53
Two plus	0	3	7	1	9	3	1	24
Three plus	0	1	3	1	1	1	0	7
Four plus	0	0	0	0	0	1	3	4
Slight junctional proliferation								
No pigment	0	0	0	0	0	0	0	0
One plus	1	2	1	3	0	0	0	7
Two plus	0	6	3	1	1	2	0	13
Three plus	0	1	1	1	2	0	0	5
Four plus	0	1	0	0	0	0	0	1
Moderate junctional proliferation								
No pigment	0	0	0	0	0	0	0	0
One plus	1	0	0	2	1	0	0	4
Two plus	3	5	1	0	0	2	0	11
Three plus	3	1	2	0	0	0	0	6
Four plus	2	3	0	0	0	0	0	5
Marked junctional proliferation								
No pigment	1	0	0	0	0	0	0	1
One plus	1	0	1	0	0	0	0	2
Two plus	3	2	2	2	0	0	0	9
Three plus	11	3	0	1	1	0	0	16
Four plus	2	0	0	0	0	0	0	2
Totals								
No pigment	1	0	0	6	8	9	7	31
One plus	5	6	13	12	12	11	7	66
Two plus	6	16	13	4	10	7	1	57
Three plus	14	6	6	3	4	1	0	34
Four plus	4	4	0	0	0	1	3	12
	30	32	32	25	34	29	18	200

the superficial part of the nevus, suggests that pigment is discharged from cells but actual death and phagocytosis of pigmented nevus cells would produce the same effect. Whether the deeper cells have lost, or never had, the property of pigment production in these sites cannot be answered from the above observations.

Multinucleated Cells. Multinucleated cells are common in nevi. Occasionally their presence or absence is carefully noted in the differentia-

tion of a nevus from melanoblastoma (Becker,[22] Dawson[23]), but the reader does not gain a clear idea of their special significance and is left with the impression that they indicate melanoblastoma. Spitz,[19] however, stressed the importance of the presence of giant cells in "juvenile melanoma," which distinguished them from "adult melanoma" in about half the cases.

It was found that multinucleated cells are of two types. The first appears as a comparatively small cluster of nuclei. In some instances these appear to lie in a common cytoplasm. In others this is not certain and the multinucleated cell may actually be an aggregate of cells, distinguished from other aggregates only by the small circular pattern of the nuclear cluster. Frequently the nuclei are densely stained, vacuolated, or distorted, appearing in curved or irregular shapes. A multinucleated cell of the second type is large and the cytoplasm is distinct. Usually the nuclei are in a peripheral ring but may be arranged in central clusters. Nuclei are not pyknotic. The chromatin pattern is delicate and sometimes there is a nucleolus. These giant cells are usually in the superficial part of the nevus.

The occurrence of multinucleated cells of both types, according to age and location, is seen in Table XI. There is no significant change in the

TABLE XI

Giant Cells of Both Kinds

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and neck								
None	4	6	1	2	5	4	4	26
Scarce	1	2	1	2	2	1	2	11
Many	4	2	6	4	1	6	3	26
Trunk								
None	13	6	3	5	6	6	3	42
Scarce	0	4	7	1	3	2	4	21
Many	1	2	1	1	1	1	1	8
Extremities, proximal								
None	2	2	3	3	3	3	1	17
Scarce	0	1	2	0	4	1	0	8
Many	0	1	1	1	2	1	0	6
Extremities, distal								
None	3	5	4	6	6	1	0	25
Scarce	2	1	2	0	1	3	0	9
Many	0	0	1	0	0	0	0	1
Totals								
None	22	19	11	16	20	14	8	110
Scarce	3	8	12	3	10	7	6	49
Many	5	5	9	6	4	8	4	41
	30	32	32	25	34	29	18	200

incidence throughout life. They are most abundant in nevi of the head and neck, and least in the nevi of the distal parts of the extremities.

The occurrence of multinucleated cells of the second type, according to age and location, is seen in Table XII. Here again, there is no sig-

TABLE XII

Large Giant Cells

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and neck								
None	7	8	5	7	6	9	8	50
Scarce	1	1	2	1	2	1	0	8
Many	1	1	1	0	0	1	1	5
Trunk								
None	14	8	7	5	8	9	8	59
Scarce	0	3	4	2	1	0	0	10
Many	0	1	0	0	1	0	0	2
Extremities, proximal								
None	2	3	5	4	5	4	1	24
Scarce	0	0	1	0	3	0	0	4
Many	0	1	0	0	1	1	0	3
Extremities, distal								
None	4	5	6	6	7	4	0	32
Scarce	1	1	1	0	0	0	0	3
Many	0	0	0	0	0	0	0	0
Totals								
None	27	24	23	22	26	26	17	165
Scarce	2	5	8	3	6	1	0	25
Many	1	3	1	0	2	2	1	10
	30	32	32	25	34	29	18	200

nificant change throughout life. The cells are least common in nevi of the distal parts of the extremities and most common in nevi of the head and neck, and proximal parts of the extremities. It is to be expected that giant cells of both types would be less numerous in nevi of the distal parts of the extremities because these are usually "narrow stratified" nevi and cells of all types are fewer in them than in the bulky nevi of other sites.

Inflammation. The nevi were studied as to the degree of inflammation present in and around each of them. This was arbitrarily subdivided as none or questionable, slight, moderate, and marked. Almost every inflammatory lesion was of chronic or subacute nature. In 4 cases the inflammation was acute exudative. In 2 of these there was ulceration. For simplification, all types are grouped and differentiated only as to degree. The results are shown in Table XIII.

It is seen that inflammation is more common in the older age groups

and is infrequent in the first decade. There is therefore no parallelism between inflammation and active (benign) proliferation of a nevus. Inflammation was more frequent and more active in the larger nevi and especially in those with large hair follicles. The follicles in nevi are often

TABLE XIII
Inflammation

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and neck								
None	8	4	3	3	3	1	2	24
Slight	0	2	3	3	4	5	3	20
Moderate	1	4	2	2	1	4	4	18
Marked	0	0	0	0	0	1	0	1
Trunk								
None	10	4	5	5	5	6	2	37
Slight	0	6	5	2	4	3	4	24
Moderate	0	0	1	0	0	0	2	3
Marked	0	2	0	0	1	0	0	3
Extremities, proximal								
None	2	4	4	0	5	4	1	20
Slight	0	0	1	4	2	1	0	8
Moderate	0	0	0	0	2	0	0	2
Marked	0	0	1	0	0	0	0	1
Extremities, distal								
None	8	5	3	6	5	2	0	29
Slight	0	1	3	0	2	1	0	7
Moderate	1	0	1	0	0	0	0	2
Marked	0	0	0	0	0	1	0	1
Totals								
None	28	17	15	14	18	13	5	110
Slight	0	9	12	9	12	10	7	59
Moderate	2	4	4	2	3	4	6	25
Marked	0	2	1	0	1	2	0	6
	30	32	32	25	34	29	18	200

dilated and filled with keratin débris. There is associated with this in many instances a perifollicular or intrafollicular leukocytic infiltration and exudation. The cells are principally lymphocytes but occasionally eosinophils and neutrophils are present. Occasionally there are foreign body giant cells. Infiltration of lymphocytes, not associated with follicles, is usually most noticeable at the lateral margins of nevi close to the surface of the normal skin. Less frequently, it is at the deep margin. It is difficult to detect slight degrees of lymphocytic infiltration or fibroblastic proliferation, for they are often closely imitated by the nevus cells. Next to lymphocytes, eosinophils were the most common form of leukocyte.

Inflammation may occur in any site. The greatest frequency is in nevi of the head and neck, evidently because of the large number of hair

follicles present. It is least common in nevi of the extremities, especially of the distal parts. This is partly explained by the large percentage of hairless nevi of the distal extremities and by the preponderance of flat ("narrow stratified") nevi which are less subject to trauma. These observations are contrary to widespread beliefs.

Inflammation has been stressed as an important sign of melanoblastoma (Miescher[8]), but from the above it is evident that many other factors must be considered. However, its presence in a flat hairless nevus is more significant than in a large nevus with numerous hair follicles.

Vascular Changes. In large nevi, especially of adult life, and nevi which tend to be pedunculated, dilatation of capillaries, venules, and lymphatics is conspicuous. In addition, interstitial edema is noted occasionally. Often the nevus cells are spread apart and lacunae suggest acini or channels. Rarely the faintly staining fluid precipitates in these spaces. Usually the above changes occur in nevi which are at least partly fibrillar. Unna's[1,2] concept that the atrophy of nevus cells and fibril formation ("molluscoid" changes) are directly related to constriction at the base and lymph edema is to be considered. However, fibrillar changes in flat nevi and nonpedunculated nevi with or without vascular dilatation are hardly compatible with this theory. Yet, that trophic disturbance may account for the later changes in nevi cannot be denied.

Miscellaneous Observations. Focal ossification in the subcutaneous fat was noted in 2 cases, and focal calcification of the subcutaneous fat in one case.

One nevus of the back of a 10-year-old child had been treated by irradiation. Because of subsequent dermatitis and ulceration the lesion was excised widely. The nevus was benign histologically but the dermatitis was complicated by squamous cell carcinoma. The case was followed for 18 years without recurrence or metastasis.

In the first part of this investigation certain features of nevi were analyzed as they relate to age and anatomic site. In order to facilitate further discussion, a summary of certain trends is advantageous.

Four features were greatly influenced by age: junctional and intraepidermal cellular proliferation, mitotic figures, size (or total cellularity), and differentiation of nevus cells to fibrillar forms. In order to simplify further discussion, the nevi have been re-evaluated and segregated into five types, determined by the above features with the exception of the presence of mitotic figures. The types are labelled A, B, C, D, and E. The characteristics of these types are:

A. The nevus consists mostly of intra-epidermal cells and cells at the dermo-epidermal junction. This includes, of course, intra-epidermal cells along hair follicles and sweat glands. There are few nevus cells in the corium.

B. The nevus consists of intra-epidermal cells and cells at the dermo-epidermal junction and there are nevus cells in fair number in the corium.

C. The nevus consists mostly of nevus cells in the corium but there is still moderate to marked cellular proliferation in the epidermis or at the dermo-epidermal junction.

D. The nevus consists of nevus cells and there is no, or very little, junctional proliferation.

E. This corresponds to type D except that many of the nevus cells are fibrillar in type.

The general trend in regard to the appearance of nevi at different ages is summarized in Table XIV. It is seen that there is a definite trend from the A type to the E type and that the age of the patient can be correlated roughly with the structure of the nevus. However, there are exceptions and these will be discussed subsequently.

TABLE XIV

Distribution of Nevi as to Type at Different Ages

Age group (*years*)	Type of nevus					Total
	A	B	C	D	E	
0–4	3	6	3	1	0	13
5–9	3	8	4	2	0	17
10–14	2	2	6	6	0	16
15–19	0	1	2	10	3	16
20–29	1	1	3	13	14	32
30–39	1	2	2	6	14	25
40–49	0	0	2	8	24	34
50–59	0	0	2	6	21	29
60–	0	0	0	2	16	18
Totals	10	20	24	54	92	200

Appearance of Multiple Nevi. In those instances in which multiple nevi from the same patient were removed at the same time the microscopic appearance was practically identical. These are analyzed in Table XV. In only one case was there notable variation, in which instance one nevus was of type A and one of type D.

Duration of Nevi. Data concerning the patients' ideas of the duration of the nevi were obtained in 87.5 per cent of the cases. Of these, 157 nevi or 89.7 per cent were stated to have been present since birth or childhood, or, in adults, for an indefinitely long period of time. Hence the trend noted above correlates with the duration of the nevus as well as with the age of the patient.

In 18 instances the nevi were stated to be of significantly shorter duration than the age of the patients. These are analyzed in Table XVI.

It may be suspected from the trend described that nevi of shorter duration in adults should resemble the nevi of childhood. However,

TABLE XV

Cases of Multiple Nevi Analyzed According to Type

	Age group (*years*)						
	0–9	10–19	20–29	30–39	40–49	50–59	60–
Number	3	1	1	3	4	1	1
Combination of types	CAA BB DD	ED	DA	AC EE CB	EE EE ED DC	EE	EE

this conclusion is not substantiated. Most of these nevi correspond in type to those which date from birth or childhood. In many instances the histories are questionable. It does not seem right that a large nevus composed often of fibrillar cells should be present only a matter of

TABLE XVI

Analysis of Nevi Stated to Be of Significantly Shorter Duration than Age of Patient

Case no.	Type of nevus	Age	Location	Reason removed	Stated duration	Recent growth	Follow-up
32	D	18	Behind ear	Growth	2–3 mos.	Yes	7 yrs.
64	D	23	Nose	Unknown	6 mos.	Yes	4 yrs.
70	E	29	Behind ear	Annoying when put glasses on	10 yrs.	Yes	2 yrs.
80	D	27	Breast	Incidental	2 yrs.	Yes	4 yrs.
81	E	27	Perineum	Incidental	6 mos.	No	9 yrs.
97	E	33	Scalp	Interfered with combing of hair	Months	Yes	4 yrs.
98	E	33	Scalp	Interfered with combing of hair	Months	Yes	4 yrs.
105	E	34	Back	Incidental	8 yrs.	None in last 3 yrs.	4 yrs.
115	A	37	Sole	Incidental	1 yr.	Yes*	1 yr.
119	B	36	Sole	Recent appearance	Few days	Yes	1 yr.
126	E	43	Chin	Incidental	4 or 5 yrs.	Yes	3 yrs.
149	D	41	Toe	Irritation	10 yrs.	Yes	6 yrs.
150	C	41	Toe	Irritation	10 yrs.	Yes	6 yrs.
176	E	56	Shoulder	Incidental	2 yrs.	No	12 yrs.
184	E	74	Neck	Growth	6 yrs.	Yes	5 yrs.
185	E	61	Canal of ear	Growth and pain	15 yrs.	Yes	5 yrs.
186	E	65	Face	Growth	1 yr.	Yes	5 yrs.
187	E	60	Eyelid	Growth	5 yrs.	Yes	13 yrs.

* Classed as recent growth because of recent appearance.

months or a few years, as was stated in some instances. It may be, as is the case in nevi of the scalp, back, auditory canal, behind the ear, or on the perineum, that the patients were not aware of the presence of the nevi for the greater part of their lives. Furthermore, since some were removed incidental to other surgical procedures, the patient may not

have been aware of the nevus at any time. The 3 nevi more in keeping with those of childhood (types A, B, and C) were of the feet.

Clinical Symptoms in Relation to Location of Nevus and Type of Nevus. The major clinical manifestations were grouped under the following headings: growth, irritation, incidental, and other manifestations. Historical details in the records usually were scanty and interview with the patient often added little information. In most instances the rate of growth was not specified or was poorly described. It was decided that the major classification should be based on the reason for removal of the nevus. Thus, if accelerated growth were the reason for removal it may be accepted that the growth was recent and appreciable. Recent appearance amnestically is considered evidence of recent growth. By irritation is meant soreness, ulceration, or bleeding. By incidental manifestations are meant such circumstances as removal in the course of other surgical procedures, for cosmetic reasons, or as a precautionary measure to avoid melanoblastoma, or because of location. Some nevi of the feet were removed for no other reason than location. In the group called "other manifestations" there was a variety of reasons, including x-ray dermatitis from previous efforts to destroy the nevus, removal in order to fit on glasses, shoe, or football helmet, and interference with combing the hair.

The reasons for removal were subdivided and compared with age and anatomic site, as shown in Table XVII.

Nevi of childhood were removed more frequently because of growth than nevi of adults. Nevi of the distal parts of the extremities were removed because of growth more often than nevi elsewhere. Nevi of the head and neck were next in this regard. The greatest single category in all anatomic sites is incidental removal. However, this accounts for the great majority of those of the trunk and proximal parts of the extremities but for less than one-half of those of the head and distal parts of the extremities. The frequent incidental removal of nevi during abdominal and perineal operations and during delivery accounts for this. Irritation is about equally important as a complaint in regard to all anatomic sites. It is a common complaint in youth as concerns nevi of the trunk but not so in middle and old age. It is a frequent complaint in reference to nevi of the head and neck in adult life and old age, but this is not true of these nevi in youth.

The histologic appearance of the nevus was compared with the major complaint and other symptoms as shown in Table XVIII.

From the totals of all ages it is construed that growth is characteristic of nevi in types A, B, and C. There is alleged growth in other types

TABLE XVII

Reasons for Removal of Nevus as Related to Site and Age

	Age group (*years*)							
	0–9	10–19	20–29	30–39	40–49	50–59	60–	Total
Head and neck								
Growth	5	2	1	0	0	5	5	18
Irritation	1	0	0	2	1	1	1	6
Incidental	3	7	3	2	6	5	2	28
Other	0	0	0	2	1	0	1	4
Unknown	0	1	4	2	0	0	0	7
Trunk								
Growth	4	0	0	1	2	0	0	7
Irritation	3	4	2	0	0	0	1	10
Incidental	3	7	8	6	8	9	5	46
Other	0	1	0	0	0	0	0	1
Unknown	0	0	1	0	0	0	2	3
Extremities, proximal								
Growth	1	1	1	0	0	0	0	3
Irritation	0	1	0	1	4	0	0	6
Incidental	0	2	5	3	5	5	1	21
Other	1	0	0	0	0	0	0	1
Unknown	0	0	0	0	0	0	0	0
Extremities, distal								
Growth	6	0	0	2	1	2	0	11
Irritation	1	2	1	0	3	0	0	7
Incidental	2	4	3	3	3	2	0	17
Other	0	0	0	0	0	0	0	0
Unknown	0	0	3	1	0	0	0	4
	30	32	32	25	34	29	18	200

TABLE XVIII

Clinical Features as Related to Type of Nevus (Total for All Ages)

Reason removed		Other features		Type of nevus				
				A	B	C	D	E
Growth	39	None	36	2	11	6	4	13
		Irritation	2	0	0	0	1	1
		Other	1	0	0	0	0	1
Irritation	29	None	22	2	1	4	7	8
		Growth	7	1	1	1	2	2
Incidental	112	None	86	2	6	12	24	42
		Growth	11	1	1	0	4	5
		Growth and irritation	2	0	0	0	2	0
		Irritation	2	0	0	0	0	2
		Unknown	11	0	0	0	3	8
Other	6	None	3	1	0	0	0	2
		Growth	2	0	0	0	0	2
		Unknown	1	0	0	0	1	0
Unknown	14	Unknown	13	1	0	1	5	6
		Growth	1	0	0	0	1	0
Totals	200		200	10	20	24	54	92

(D and E) but less often. However, types A, B, and C are characteristic of the first decade in which the common feature is growth. Further analysis of the symptoms as they relate to each age period demonstrates that in any one decade the nevi, no matter what the complaint, are very much alike. The charting of this analysis is lengthy and is not included in this paper.

Nevi of the E type are comparatively acellular and it is reasonable to assume that growth relates to fibrillar proliferation.

Nevi Which Deviate Histologically from the Trend. Certain deviations from the trend were mentioned earlier in this analysis and they are readily seen in Table XIV. These deviations are of two types: (I) those occurring in children but resembling nevi of adults (types D and E), and (II) those occurring in adults but resembling those usual in childhood (types A, B, and C). These are analyzed in Table XIX.

No special conclusion can be drawn concerning the first group. Either certain nevi "mature" more rapidly than usual and proliferation at the dermo-epidermal junction ceases early or the growth of nevus cells is entirely from deep sites. Serial sections would probably be enlightening in these cases, but these were not made.

The second group is of more clinical interest. The first 5 cases are in the second decade and are not striking deviations from the trend. From them, however, it is evident that nevi of types A and B may have a duration of at least a decade. All of these nevi date from birth. It is to be noted that nevi of the feet or hands are represented in 3 of these 5 cases. There are 2 cases of type A nevi in adult life. One, from the foot, was stated to be of 1 year's duration. No history was available in the other, which was from the hand. There were 3 type B nevi in adults, of which one was stated to be present since birth, one for 15 years, and one had been noted only a few days. All were present on the feet. The type C group in adults is more variable in location. Four were from toes, 1 from axilla, 1 from abdomen, 1 from elbow, 1 from cheek and 1 from back. All are said to have been present since birth or childhood, or for a long period of time.

In an analysis of age groups beyond 20 years, it is found that the frequency of active growth in nevi which deviate from the trend is greater than the average for all other nevi of adults. In the group which deviates from the trend, 5 of 12 cases in which information was available, or 42 per cent, listed this feature. This is to be compared with 32 of 104, or 31 per cent, in other nevi of adults. These differences are not statistically significant.

The series is too small for conclusions and study of a larger group is

TABLE XIX

Nevi Which Histologically Deviate from Trend

Case no.	Type of nevus	Age	Location	Reason for removal	Stated duration	Recent growth	Follow-up
				Group I			
3	D	3	Forehead	Growth	Since birth	Yes	10 yrs.
6	E	9	Neck	Irritation	Since birth	No	1 yr.
17	E	9	Back	Growth	Since birth	Yes	1 yr.
36	E	16	Face	Cosmetic	As long as can remember	No	2 yrs.
44	E	17	Back	Incidental	Unknown	Unknown	Unknown
45	E	17	Back	Irritation	As long as can remember	No	13 yrs.
				Group II			
42	B	17	Pubic region	Incidental	Since birth	No	11 yrs.
46	B	10	Abdomen	Incidental	Since birth	No	12 yrs.
59	B	13	3rd toe	Incidental	Since birth	No	19 yrs.
61	A	12	Foot	Incidental	Since birth	No	1 yr.
62	A	12	Palm	Exposed to trauma	Since birth	Yes	6 mos.
67	A	25	Hand	Unknown	Unknown	Unknown	Unknown
92	B	29	5th toe	Irritation	15 yrs.	No	5 yrs.
72	C	24	Axilla	Irritation	Since birth	No	5 yrs.
78	C	27	Abdomen	Incidental	Since birth	No	8 yrs.
93	C	27	Elbow	Unknown	Since birth	No	8 yrs.
115	A	37	Sole	Incidental	1 yr.	Yes*	1 yr.
116	C	37	Toe	Incidental	Since childhood	No	1 yr.
117	C	30	Toe	Growth	Since birth	Yes	2 yrs.
118	B	30	Toe	Incidental	Since birth	No	2 yrs.
119	B	36	Sole	Recent appearance	Few days	Yes	1 yr.
147	C	42	Between 2nd and 3rd toes	Growth	Since birth	Yes	8 yrs.
150	C	41	Toe	Irritation	10 yrs.	Yes	6 yrs.
154	C	50	Cheek	Incidental	Since birth	No	8 yrs.
169	C	59	Back	Incidental	More than 20 yrs.	No	17 yrs.

* Classed as recent growth because of recent appearance.

indicated. If the patients' histories are correct there is no clear-cut rule, for some of these nevi were stated to be of short duration and others were stated to have been present since birth or childhood, or for an indefinitely long period. However, of the 4 nevi of adults of types A and B in which there is clinical information, there is only one which is stated to have been present since birth. Of the C type, 6 of 9 were said to have been present from birth. This is not appreciably lower than the average of the entire series.

Nevi of Hands and Feet. Nevi which deviate from the trend are commonly of the hands and feet, and a separate analysis of these is indicated. The peculiar tendencies of nevi of the distal parts of the extremities to be of the flat ("narrow stratified") type with junctional proliferation in adult life have been noted earlier in this study. Nevertheless, it was shown that there are similarities in the trend to nevi in general. In Table XX the analysis is confined to nevi of the hands and feet, omitting legs and forearms.

In patients beyond the age of 20 years there is a higher incidence of history of growth (including recent appearance) than for all other nevi in adults. For those with nevi of the hands and feet there were 7 of 17, or 41 per cent, who gave this history, while for all other nevi of adults for which there was the necessary information there were 30 of 99, or 30 per cent. In such a small series the difference is not significant.

The incidence, in adults, of short duration is a little higher in this group of nevi than with nevi of other locations. In 4 of 17, or 23.5 per cent, of these cases in which there is clinical information, the duration was significantly shorter than the age of the patient. This is to be compared with 13 of 99 cases, or 13 per cent, in all other nevi of adults in which there is clinical information. The series is small and the difference is not significant.

The above data concerning growth and duration must be weighted by the consideration that there is a special selection for surgical removal in these cases. Nevi of the feet and hands were less frequently removed incidentally and more frequently removed because the patient was aware of growth. In contrast, in cases of nevi of the thorax which were often removed incidentally during an abdominal operation, the patient may not have been aware of the nevus and its growth characteristics.

The eventual trend of nevi of hands and feet in this series is shown in Table XXI which summarizes the appearance of nevi of hands and feet of all ages. It is seen that among nevi located on hands or feet there is a trend toward diminution of the incidence of types A, B, and C between the ages of 40 and 50, and increase of incidence of types D and E. Thus,

TABLE XX

Analysis of Nevi of Hands and Fingers, Feet and Toes

Case no.	Type of nevus	Age	Location	Reason for removal	Stated duration	Recent growth	Follow-up
				Age 0–9 years			
27	B	6	Under toe	Growth	Since birth	Yes	7 yrs.
30	B	2	Hand	Irritation	Since birth	Yes	6 mos.
				Age 10–19 years			
57	D	14	Dorsum hand	Incidental	Since birth	No	7 yrs.
58	C	12	Dorsum foot	Bleeding and irritation	Since birth	No	15 yrs.
59	B	13	3rd toe	Incidental	Since birth	No	19 yrs.
60	D	12	Sole	Incidental	Since birth	No	1 yr.
61	A	12	Foot	Incidental	Since birth	No	1 yr.
62	A	12	Palm	Exposed to trauma	Since birth	Yes	6 mos.
				Age 20–29 years			
89	E	21	Thumb	Prophylactic and cosmetic	Since childhood	No	3 yrs.
90	D	25	Toe	Unknown	Unknown	Unknown	Unknown
91	A	25	Hand	Unknown	Unknown	Unknown	Unknown
92	B	29	5th toe	Irritation	15 yrs.	No	5 yrs.
94	D	29	Under 2nd toe	Incidental	Since birth	No	1 yr.
				Age 30–39 years			
115	A	37	Sole	Incidental	1 yr.	Yes*	1 yr.
116	C	37	Toe	Incidental	Since childhood	No	1 yr.
117	C	30	Toe	Growth	Since birth	Yes	2 yrs.
118	B	30	Toe	Incidental	Since birth	No	2 yrs.
119	B	36	Sole	Recent appearance	Few days	Yes	1 yr.
				Age 40–49 years			
147	C	42	Between 2nd and 3rd toes	Growth	Since birth	Yes	8 yrs.
148	E	48	Toe	Incidental	20 yrs.	No	4 yrs.
149	D	41	Toe	Irritation	10 yrs.	Yes	6 yrs.
150	C	41	Sole	Irritation	10 yrs.	Yes	6 yrs.
151	D	48	Sole	Irritation	A number of yrs.	No	5 yrs.
152	D	40	Toe	Incidental	As long as can remember	No	1 yr.
153	E	44	Hand	Incidental	10 or more yrs.	No	10 yrs.
				Age 50–59 years			
179	E	51	Between toes	Growth	Since birth	Yes	13 yrs.
181	D	53	Under great toe	Incidental	Since birth	No	10 yrs.

* Classed as recent growth because of recent appearance.

in this series there is an eventual trend for nevi of hands and feet to lose junctional proliferation and for the cells to differentiate to fibrillar forms, although usually at an older age than is true of nevi of other sites. Study of a larger series of nevi of hands and feet is indicated for these results are not conclusive. It is disturbing that there is a scarcity

TABLE XXI

Summary of Histologic Appearance of Nevi of the Hands and Feet at Different Ages

Age group (years)	Type of nevus				
	A	B	C	D	E
0–4	0	1	0	0	0
5–9	0	1	0	0	0
10–14	2	1	1	2	0
15–19	No cases				
20–29	1	1	0	2	1
30–39	1	2	2	0	0
40–49	0	0	2	3	2
50–59	0	0	0	1	1
60–	No cases				

of benign nevi from the hands and feet of patients older than 50 years (we obtained only 2 cases), yet melanoblastomas are common in these sites. Undoubtedly the number is modified by the reasons for removal of a nevus. Most nevi in this series were removed incidentally and incidental removal of a nevus of the hand or foot during a major surgical operation will occur but rarely. Further, if a patient has tolerated such a nevus for 40 or 50 years he probably will not have it removed for cosmetic reasons.

Significance of Junctional Proliferation in Nevi of Adults. As pointed out earlier, the data thus far presented comprise only the first step in the analysis of this problem. Several points are evident at this time, however. The presence of junctional proliferation of moderate to marked degree in adult life, especially in young adult life, is to be expected in a minority of cases and of a slight degree in a greater number. There is no sharp distinction of such nevi from all others. There is no age at which junctional proliferation abruptly stops. Therefore, junctional proliferation does not in itself mean a "precancerous" state. A marked deviation from the trend, however, in the degree of this proliferation or in the presence of other variations, as noted in the next paragraph, raises the question of melanoblastoma.

Nevi, of adults, which consist of junctional and intra-epidermal cells almost entirely (type A), are disturbing to the pathologist and although the data submitted do not fully substantiate the conclusion in all instances, it is still suspected that these histologic characteristics indicate recent origin and growth. The other alternative is that a nevus resembling

that of early childhood can persist without further differentiation for as long as 30 to 40 years. Finding nevi (benign) of this type after age 40 is decidedly infrequent. Although the pathologist is guarded in excluding melanoblastoma in these cases, it is thought that until more conclusive evidence is obtained, such a diagnosis must rest on additional observations, including (a) excessively large, irregularly scattered or otherwise bizarre masses or nests of cells at the dermo-epidermal junction, (b) deep penetration of large cells without differentiation to small nevus cells and fibrillar forms, (c) more mitotic figures than are usual, (d) atypical and pleomorphic cells, (e) invasion, and (f) inflammation, other than folliculitis, which is not accounted for by trauma.

Summary

There are progressive changes in the histologic appearance of nevi throughout life. The features which change most noticeably are size, number of nevus cells, proliferation of cells in the epidermis and at the dermo-epidermal junction, number of mitotic figures, and presence of fibrils and nerve-like elements. In most instances, an approximate correlation of the histologic appearance with the age of the patient can be made by an evaluation of these features.

Judged from the transitions noted in the different age groups, nevus cells appear to differentiate slowly from foci of clear cells found in the epidermis and follicles and along sweat glands. Further differentiation, principally in adult life, leads to the formation of fusiform cells with fibrils which in many instances resemble neurofibrils and tactile corpuscles. Such structures are therefore to be considered the final stage of differentiation of nevus cells, not the source of nevus cells. That the foci in the epidermis, follicles, and sweat glands are the only source of nevus cells is favored but not proved.

There are exceptions to the general trend. Nevi of children may resemble those of early adult life. Nevi of adults, usually in the third and fourth decades, may resemble nevi of childhood. The latter exception is notable in regard to nevi of the hands and feet. However, in this series the trend of nevi in middle age in these sites is similar to the trend of nevi in general. Final conclusions must be based on a larger series.

Junctional proliferation in nevi of adults does not in itself indicate melanoblastoma. There are an expected incidence and degree of such proliferation at various ages. Certain additional criteria must be fulfilled before a histologic diagnosis of melanoblastoma is warranted.

In adults the occurrence of nevi which morphologically resemble those of childhood leads to the suspicion that they are incipient and

growing, but clinical evidence obtained in this analysis of their duration and rate of growth is variable and conflicting, permitting no final conclusion. Evaluation must await further study.

Nevi vary in appearance according to location. A notable modifying factor is the number of hair follicles and sweat glands in the various cutaneous sites. While most nevi have nevus cells in a superficial stratum beneath the epidermis, deeply placed nevus cells tend to have a perifollicular and periglandular distribution. Diffusely scattered, deeply placed nevus cells also occur.

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[*Illustrations follow*]

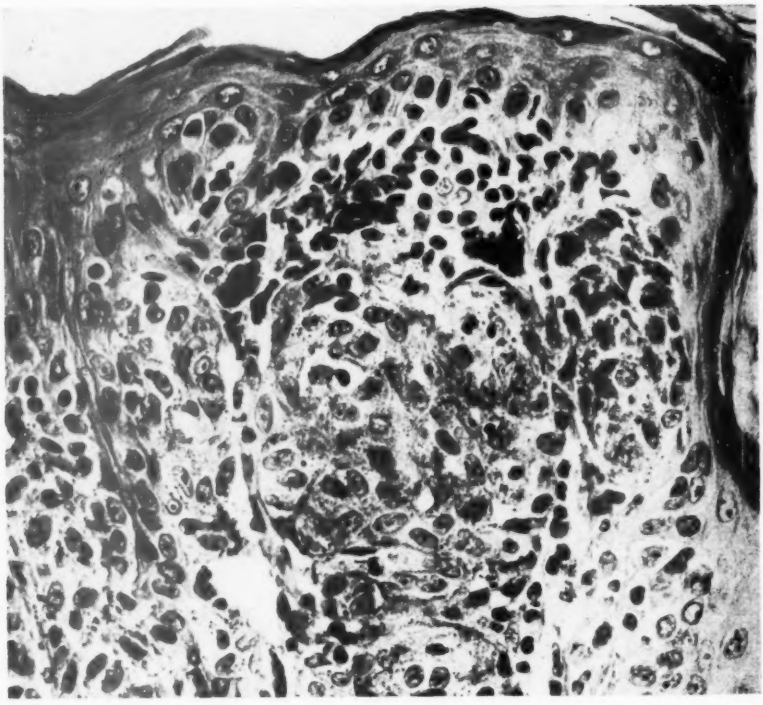
DESCRIPTION OF PLATES

PLATE 177

FIG. 1. Nevus of abdomen of a male, 6 years of age. There is proliferation of large pigmented cells at and beneath the dermo-epidermal junction. One mitotic figure is shown. × 445.

FIG. 2. Nevus of thorax of a female, 42 years old. Fibrillar structures resemble tactile corpuscles. × 312.

1



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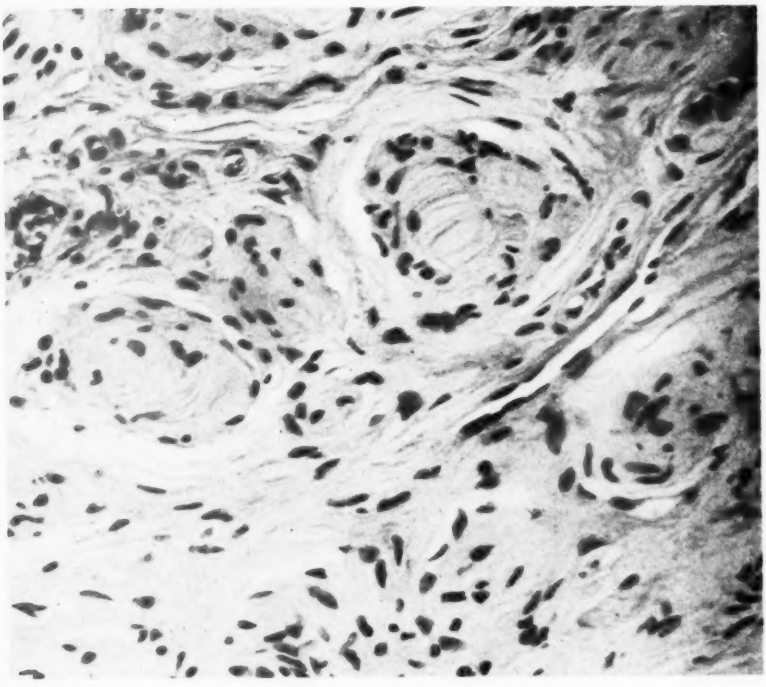


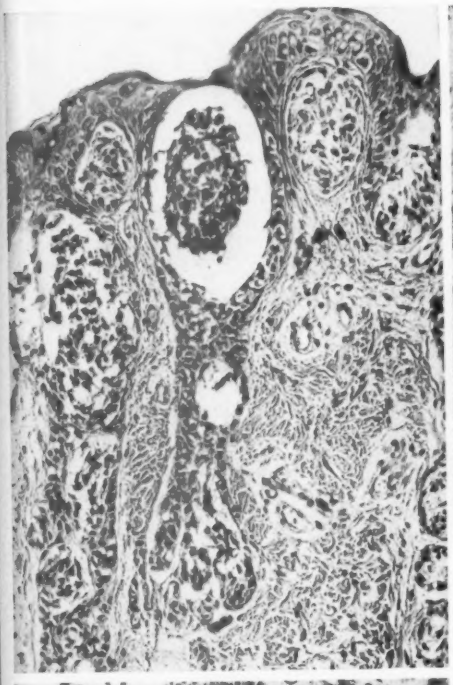
PLATE 178

FIG. 3. Nevus of face of a female, aged 12 weeks. Clear cells are present in clumps within the epidermis and along the hair follicles. × 154.

FIG. 4. Nevus of a female, 37 years old. Small round nevus cells and fusiform fibrillar nevus cells are present. × 186.

FIG. 5. Nevus of thorax of a male, aged 6 years. Clear cells occur in clumps along a sweat gland. × 169.

FIG. 6. Nevus of scalp of a female, 18 years of age, with nevus cells distributed about a sweat gland.



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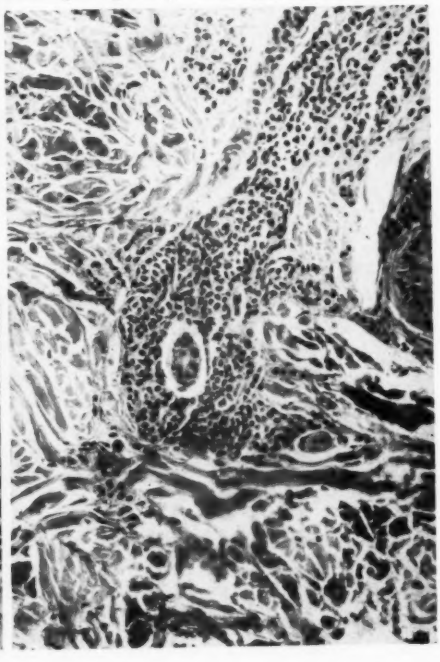


6

Lund and Stobbe

Natural History of the Pigmented Nevus

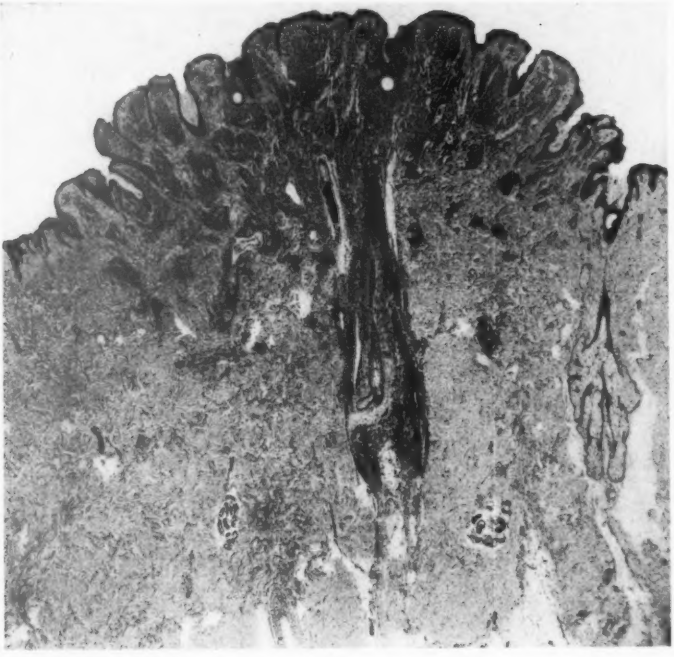
PLATE 179

FIG. 7. Nevus of neck of a female, 19 years old. The deep cells have a perifollicular distribution. × 18.

FIG. 8. Nevus of lower eyelid of a male, aged 22 years. Nevus cells are found among striated muscle fibers. There has been no recurrence in 18 years. × 109.

XEROX

7



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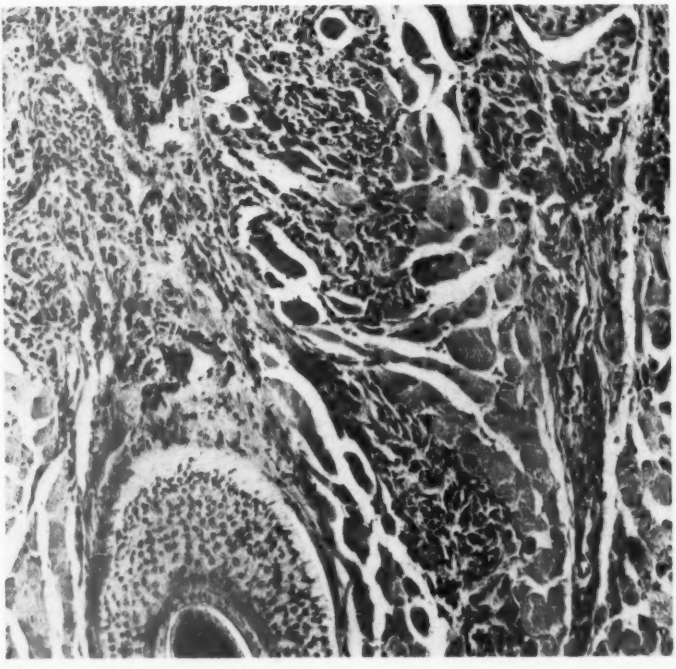


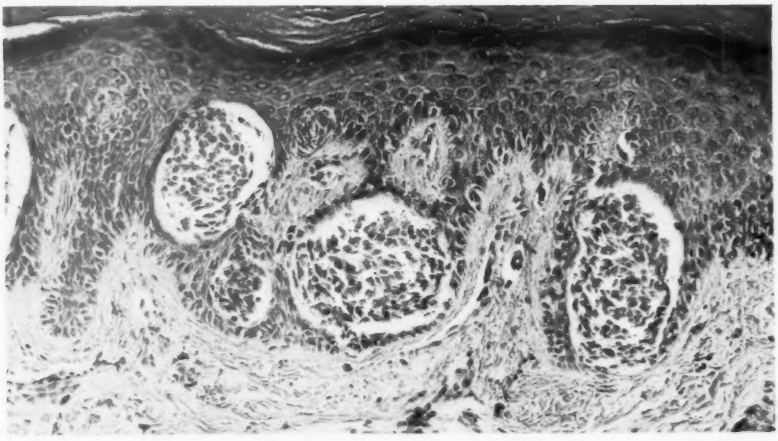
PLATE 180

FIG. 9. Nevus of sole of a female, 37 years of age. Clear cells are present in clumps in epidermis. No nevus cells are found in the corium. × 150.

FIG. 10. Nevus of sole of a female, 48 years of age. Nevus cells are present in the corium. There is slight dermo-epidermal proliferation. × 150.

FIG. 11. Nevus between toes of a male, aged 41 years. Nevus cells are present in the corium. There is no junctional proliferation. × 79.

9



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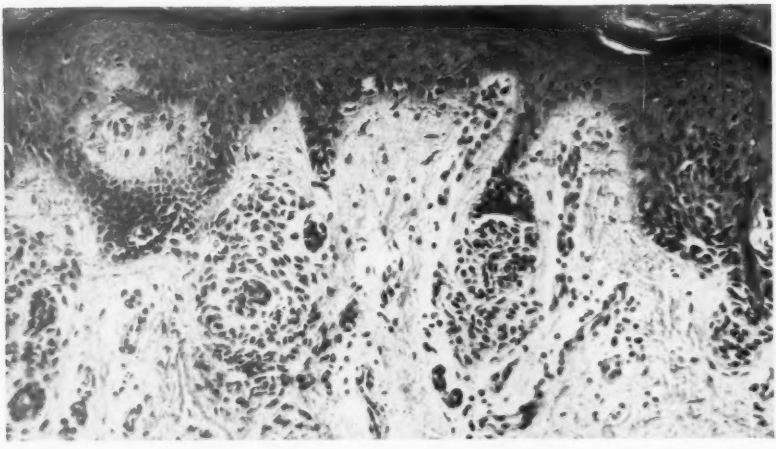

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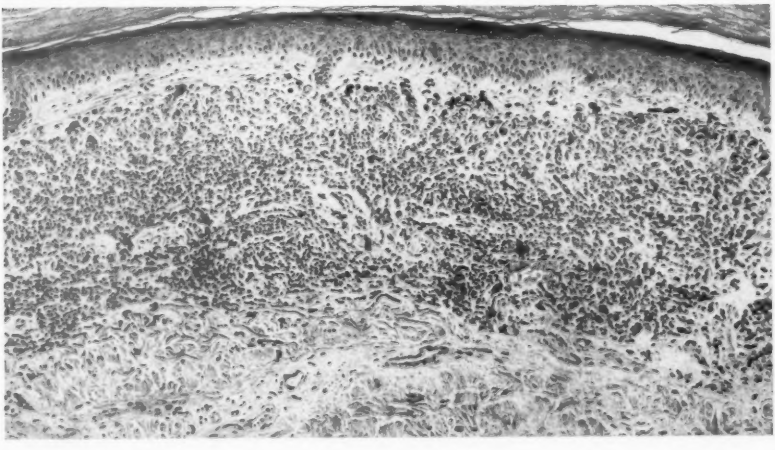

MYOBLASTOMA*

GEORGE H. MURPHY, M.D., MALCOLM B. DOCKERTY, M.D., and ALBERT C. BRODERS, M.D.
(From the Mayo Foundation and Mayo Clinic, Rochester, Minn.)

Myoblastomas are tumors consisting of large cells with granular cytoplasm which resemble myoblasts, the embryonic precursors of striated muscle fibers. These tumors are commonest in voluntary striated muscle but have been found also in sites where striated muscle is not normally present. The tumors are rare and are mostly benign. Since 1926, when the entity was first recognized, there has been controversy as to their nature, histogenesis, and possible malignancy.

In the present study 10 new cases are reported and reports of 219 other cases from the literature are reviewed.

Abrikossoff,[1] in 1926, has been credited generally with first establishing this tumor entity under the name of "Myoblastenmyome." Several authors[2-7] preceded him with case reports in which the lesions were given various names, but the tumors described are seemingly identical with the entity named and established by Abrikossoff. He was convinced that the large granular cells which made up the bulk of his tumors were identical with the embryonic striated muscle cells, the myoblasts, as depicted by Godlewski[8] in 1902 in his work on the histogenesis of striated muscle.

There have been numerous reports and reviews on this subject since publication of Abrikossoff's paper.[1] Among the more significant contributions, those of the following authors may be mentioned: Klinge,[9] Diss,[10] Meyer,[11, 12] Klemperer,[13] Gander,[14] Cappell and Montgomery,[15] Grayzel and Friedman,[16] Leroux and Delarue,[17] Holle,[18] Ringertz,[19] Horn and Stout,[20] Lauche,[21] Howe and Warren,[22] Crane and Tremblay,[23] Ravich, Stout, and Ravich,[24] Ackerman and Phelps.[25-26] As will be discussed later, the histogenesis and possible malignancy of myoblastomas have been the points of greatest interest to the various observers.

The specimens in this study were obtained from the Section on Pathologic Anatomy and the Section on Surgical Pathology of the Mayo Clinic. All had been preserved in a 10 per cent solution of formalin (3.8 per cent aqueous solution of formaldehyde gas). Sections were cut by the fixed frozen-tissue technic and from paraffin blocks. The frozen sections were stained for fat with sudan III; the paraffin blocks were stained with hematoxylin and eosin, Masson's trichrome, Bodian's stain (silver stain)

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and with a modified Mayer mucicarmine technic.[27] Early in the study some sections were stained with Mallory's phosphotungstic acid hematoxylin and also with Heidenhain's iron hematoxylin, but these yielded no further information and were not continued. Stains for glycogen were not possible because of the fixation with formalin.

Report of Cases

Case 1

A white man, 62 years of age, was admitted on September 1, 1942, for investigation of a fistula in ano. In the course of routine examination, a nodule was noted on the tip of his tongue; the patient had been unaware of its existence and had no complaints referable to the tongue. Family and past histories were irrelevant. Serologic tests for syphilis gave negative results. The nodule was excised.

Pathologic Findings. The gross appearance was not distinctive. The nodule was firm and round and measured about 0.5 cm. in diameter. It cut easily; the cut surface was homogeneous and a dirty white. There was no distinct capsule. On histologic examination, the nodule was seen to consist of large cells with coarsely granular cytoplasm and delicate, often indistinct, cell membranes (Fig. 1*a*). The nuclei were usually single; they stained lightly with hematoxylin; and each had a visible, though not unduly prominent, nucleolus. In some areas several granular cells seemed to have fused to form a syncytial mass roughly cylindric in outline and containing many nuclei. Irregularly placed between the granular cells were wisps of delicate, acellular connective tissue. The granular cells abutted against the surface epithelium and extended to, and seemed to invade, the underlying muscle. The overlying epithelium was hyperplastic and showed some parakeratosis. In the deeper part, where the granular cells apparently were invading the muscle, some seemingly degenerating muscle fibers were seen; but although the granular cells and altered muscle fibers were frequently intimately related, no actual transition from one to the other could be demonstrated. Nor were longitudinal or cross striations seen in the granular cells. The cytoplasm of the granular cells was acidophilic; in some, round bodies were noted which were 3 to 4 μ in diameter, homogeneous, and rather more acidophilic than the surrounding cytoplasm. No mitotic figures were seen.

Case 2

A white man, 52 years of age, was admitted on November 7, 1944, complaining of a painless lump on his tongue which had grown slightly since he first noticed it some 4 months previously. His mother had died from the effects of cancer of the mouth. The past history was irrelevant except that he had been an ardent chewer of tobacco. Examination revealed a round, hard, raised, nontender nodule on the right side of his tongue. Serologic tests for syphilis gave negative results. The nodule was excised.

Pathologic Findings. The excised tumor formed a firm, homogeneous, gray-white mass, 1.3 cm. in diameter, with no obvious capsule. On histologic examination the surface epithelium was seen to be markedly hyperplastic. Just beneath this epithelium was a layer of collagenous connective tissue, enmeshed in which were large polyhedral cells with granular cytoplasm and delicate cell membranes. As in case 1, areas were seen where these cells had fused to form a syncytium with numerous nuclei. The musculature of the tongue was extensively infiltrated with the granular cells and there were many altered or degenerating muscle bundles. In a single muscle bundle could be seen normal muscle fibers, altered muscle fibers, and the pale granular cells. It was difficult to evaluate the nature of the change in these "altered" muscle fibers; they stained less intensely and had lost or were losing their striations, but their nuclei were often intact and were sometimes centrally located. They may have been undergoing degeneration or possibly were regenerating as a result of minimal trauma. In some instances a single sarcolemma seemed to enclose granular cytoplasm with nuclei and rather frayed-looking striated fibers (Fig. 1*b*). In this section it seemed quite logical to assume that the degenerating or regenerating muscle fibers actually formed the granular cells. No mitotic figures were seen.

Case 3

A white woman, 36 years of age, was admitted on August 15, 1945, with varied complaints among which was that of a growth on her tongue. This had been noticed about 1 week prior to admission but, apart from creating a fear of cancer, had caused the patient no distress. Family and personal histories were irrelevant. Examination revealed a small, hard, nontender nodule on the right side of the tip of the tongue. The results of serologic tests for syphilis were negative. The nodule was excised.

Pathologic Findings. Grossly, the tumor was similar to those in cases 1 and 2. Histologic examination revealed a decidedly hyperplastic epithelium overlying a mass of the large granular cells, many of which were fused to form cylindric syncytia (Fig. 2*a*). The cytoplasm was coarsely granular and contained the amorphous round bodies noted in case 1. In the deeper part of the tumor, the granular cells seemed to infiltrate the muscle layer. No transitional forms were observed, but many of the cylindric granular masses seemed to have an alignment of their granules very suggestive of longitudinal and cross striations. No mitotic figures were noted. The connective tissue stroma was even less prominent than in cases 1 and 2.

Case 4

A white man, 41 years of age, was admitted on June 28, 1946, complaining of a painless, slowly growing mass in the left side of his tongue which had been present

for about 1 year. On examination, a hard, nontender, circumscribed mass about 0.5 cm. in diameter was noted in the left margin of the tongue. The nodule was excised.

Pathologic Findings. The excised nodule was firm and dull white on cut section which measured about 0.7 by 0.5 cm. Histologic examination revealed a picture similar to that described in case 1. There were the same aggregations of large granular cells in intimate relation to the overlying markedly hyperplastic epithelium (Fig. 2*b*) and the same infiltration of the muscle in the deeper zones. In some areas there was close contiguity of granular cells and somewhat altered muscle fibers, but no very convincing transitional forms were noted. The round, amorphous cytoplasmic inclusions were prominent in many of the granular cells. No mitotic figures were seen.

Case 5

A white man, 43 years of age, was admitted on April 15, 1947, complaining of a lump in his tongue which had been present for about 3 years. This had increased in size gradually but had not ulcerated. Early in March, 1947, his local physician had taken a specimen for biopsy and had told him he had cancer of the tongue which would require surgical treatment. Family and personal histories were irrelevant. The results of serologic tests for syphilis were negative. On examination, a hard mass measuring about 2 by 3 cm. was seen on the left anterior border of the tongue; the surface showed a whitish plaque (Fig. 3*a*). Two other plaques, each about 0.5 cm. in diameter with underlying firmness, were noted on the right side of the tongue. On April 17, 1947, a specimen was excised and diagnosed "grade 2 squamous-cell epithelioma." The next day a dissection of the submental and bilateral submaxillary nodes, including the salivary glands, was performed; no metastases were found in the tissues removed. It had been the intention to do a plastic operation on the tongue later, but the patient died rather suddenly some 16 hours after operation.

Pathologic Findings. At autopsy the cause of death was established as edema of the larynx. There were no other pertinent findings except as related to the lesions of the tongue. The larger tumor on the left side of the tongue was gray-white on cut section, with an indefinite margin (Fig. 3*b*). The two smaller plaques seemed to be limited to the surface epithelium, the underlying tissues appearing quite normal. Histologically, the main tumor was seen to consist of sheets of large, ill defined granular cells similar in all respects to those seen in the other lingual myoblastomas (Fig. 3*c*). The overlying epithelium was greatly hyperplastic and in several areas showed early squamous cell carcinoma. The tumor cells were infiltrating the underlying muscle and numerous transitional forms were noted (Fig. 3*d*). The two smaller "tumors" showed merely some epithelial hyperplasia with edema of the underlying tissues.

Case 6

A mulatto woman, 72 years of age, was admitted on October 16, 1946, with numerous complaints, mostly of senile origin. In the course of routine examination

a hard, nontender, freely movable nodule about 2 cm. in diameter was noted in the right labium majus pudendi. Family and personal histories were irrelevant. At operation the nodule was found to be attached to the overlying skin at one point but did not seem to invade the deeper tissues.

Pathologic Findings. The excised nodule measured 3.5 by 2.5 by 2 cm., was of firm consistency, and the cut surface was white. On histologic examination the nodule was seen to consist of the typical large granular cells along with a collagenous connective tissue rather more prominent than that seen in cases 1 through 5 (Fig. 4*a*). There was no striated muscle in the sections, nor could cross or longitudinal striations be demonstrated in the granular cells. The overlying skin showed a moderate degree of hyperplasia with parakeratosis, and the subepithelial layer was infiltrated with round cells which were mostly lymphocytes.

Case 7

A white woman, 37 years of age, was admitted on February 2, 1942, with numerous complaints of a neuropsychiatric nature and also of a lump behind her right ear. This nodule had been present for about 2 years but had shown recent rapid enlargement. Family and personal histories were irrelevant. Examination revealed a firm, slightly movable, subcutaneous nodule about 2 cm. in diameter just anterior to the tip of the right mastoid process. At operation the nodule was found to be densely adherent to the underlying tissue.

Pathologic Findings. Grossly, the nodule was firm, white on cut section, and measured 2.5 cm. in diameter. Histologically, it consisted of masses of large granular cells separated by a considerable amount of collagenous connective tissue and numerous thin-walled blood vessels (Fig. 4*b*). There was neither epithelium nor muscle in the sections examined. None of the granular cells showed cross or longitudinal striations, but a few slender spindle cells showed an alignment of cytoplasmic granules suggestive of striations. No mitotic figures were observed.

Case 8

A white man, 50 years of age, was admitted on February 19, 1945, complaining of the recurrence of a lump on his left arm. Three years previously in another community, a mass the size of a baseball had been removed from his left biceps muscle, and this tumor had been reported as "grade 4 sarcoma"; an axillary node removed at the same time was not involved. Family history and the remainder of the personal history were irrelevant. Examination revealed a healed scar over the belly of the left biceps; beneath the scar was a firm tumor about 2 by 5 cm. which moved with the muscle but which was not attached to the skin. No enlarged nodes could be palpated in the axilla. At operation a tumor was found embedded in the long head of the biceps; it was removed along with some surrounding, apparently healthy, muscle.

Pathologic Findings. The excised tumor was firm, fairly well circumscribed, and measured 2.5 by 2 by 2 cm. Histologic examination revealed a pleomorphic pattern dominated by large cells with granular

cytoplasm (Fig. 5*a*). These cells varied from about 20 to 50 μ in diameter. Some very finely and some coarsely granulated varieties were noted, the latter being markedly acidophilic. Some of the larger cells contained multiple nuclei and some a single, large, irregular vesicular nucleus. The nucleoli in all cells were very prominent. For the most part these granular cells were more isolated by the connective tissue stroma than those in cases 1 through 7, and they showed no tendency to fuse into syncytial masses. There was considerable edema of the connective tissue stroma and the tumor in general was quite vascular. Mitotic figures, including abnormal forms, were seen (Fig. 5*b*). The granular cells were mostly round or oval, but some of the smaller ones were spindle-shaped. Well into the center of the tumor a few bundles of striated muscle fibers were seen, but it was not possible to demonstrate any close relationship of these fibers to the granular cells. At the periphery of the tumor, muscle bundles and long, cylindric granular cell masses were intimately intermingled (Fig. 5*c*). The tumor was considered a highly malignant myoblastoma.

Course. On July 25, 1946, the patient returned with another lump near the old scar over his left biceps, and a nodule 1.5 cm. in diameter was excised. Grossly and histologically it was identical with the tumor removed at the Clinic. He returned again on June 10, 1947, with a flaccid paralysis of his right arm which had developed during the previous month. A diagnosis of metastasis to the left frontoparietal region of the brain was made in spite of negative roentgenologic findings. He was given a course of roentgen therapy and improved somewhat. Three months later, on September 12, 1947, he was readmitted with complaints of low back pain and mental confusion. This time roentgenograms of the head showed a lesion which was interpreted as a cerebral metastasis of the myoblastoma. The patient's wife refused to allow further roentgen therapy and he returned home.

Case 9

A white man, 50 years of age, was admitted on May 15, 1945, with a lump in his right hand. Five months previously he had bruised his hand slightly and afterwards noticed some stiffness of the middle and ring fingers, but roentgenograms revealed no bony changes. A few weeks later a swelling developed in the palm of his hand: this was incised but little or no pus was found. Penicillin therapy was instituted empirically with no apparent result. A biopsy performed elsewhere at this time resulted in a diagnosis of inflammatory tissue with the possibility of myxosarcoma. On examination there was a firm, freely movable, subcutaneous mass in the right palm. The overlying skin showed a bluish red discoloration. Roentgenograms showed slight osteoporosis of the metacarpals. At operation, the tumor was excised in its entirety; it was adherent to the tendon sheaths but otherwise shelled out relatively easily.

Pathologic Findings. The tumor was removed in pieces having an aggregate mass of about 5 by 4 by 4 cm.; it was firm and dull white on cut section. Histologically, it consisted of a myxocollagenous tissue matrix enclosing numerous fine spindle and stellate cells, and many

large, round or elongated cells with acidophilic granular cytoplasm (Fig. 6*a*). Some of these large granular cells had a fenestrated periphery resembling the so-called spider cells described in rhabdomyosarcoma of the heart. Most of these granular cells contained but one large, vesicular nucleus, often irregular in outline, with one or two very prominent nucleoli. No definite cross striations could be demonstrated but some of the more elongated granular cells seemed to have an arrangement of their granules suggestive of longitudinal and even cross striations. A few mitotic figures were seen in the granular cells. All sections examined showed polymorphonuclear leukocytes and lymphocytes. There was no muscle present.

Course. The patient returned on March 12, 1946, having noted a recurrence of the lump in his hand about 1 month previously. This had doubled in size during the month. On examination, a mass 1 cm. in diameter was seen in the right palm over the flexor tendon of the index finger; it was not tender and moved with the tendon. There was also an enlargement of the palmar surface of the right wrist which had been present for about 9 months, gradually increasing in size. Because the patient was a veterinarian and because of the inflammatory reaction in the original tumor, bacteriologic studies were done. Guinea-pig inoculation and smears and cultures for fungi all gave negative results. *Corynebacterium xerosis* was cultured from the wound. At operation a tumor similar to that found previously was excised; the mass in the wrist was continuous with the one over the tendon sheath of the index finger.

Pathologic Findings. The tumor was identical grossly with the one removed in 1945. It formed an aggregate about 5 cm. in diameter and weighed 29 gm. Histologically, it was similar to the original growth, but the granular cells were more numerous, many of them were larger, and there were more so-called spider cells. Longitudinal striations were noted in many of the elongated granular cells but no more than a suggestion of cross striation could be demonstrated. The stroma was denser and did not appear as myxomatous as that in the tumor removed in 1945, and there were fewer of the slender spindle and stellate cells. The tumor was adjudged a malignant myoblastoma.

Case 10

A white girl, 12 years of age, was admitted on July 3, 1929, with a lump on her left thigh. She had noticed an aching pain in her leg about 5 months previously and the lump appeared shortly thereafter; it had not increased in size. Family and personal histories were irrelevant. Examination revealed a mass about 10 cm. in diameter on the posterior aspect of the left thigh just above the knee. It was not attached to the femur and was of firm consistency. At operation the tumor was excised from its bed in the muscles of the thigh; it was quite sharply outlined and was removed with little difficulty.

Pathologic Findings. Grossly, the tumor measured 8 by 5 by 6 cm., it was firm, and the cut surface was homogeneous and gray-white. It

consisted of a meshwork of spindle cells, some of which were quite plump, and numerous large spindle or round cells with as many as four nuclei, with prominent nucleoli (Fig. 6*b*). These large cells had a finely granular cytoplasm and a suggestion of longitudinal striations, especially in the tails of the larger elongated forms; no definite cross striations were seen. The tumor had a fairly well defined capsule and there was little infiltration of the surrounding muscle in the sections examined.

TABLE I

Acceptable Cases of Myoblastoma as Reported in the Literature Listed by Year of Report, Author's Name, and Author's Case Numbers*

1854 Weber[7]
1881 Heurtaux[2]
1894 Massin[3]
1897 Pendl[5]
1922 Moschcowitz[4]
1925 Quirin[6]
1926 Abrikossoff[1]; 1, 2, 3, 4, 5
1926 Keynes[40]
1926 Rütz[41]
1927 Dewey[42]
1927 Diss[10]
1928 Klinge[9]; 5 cases
1928 Kraneis[43]; 1, 2
1928 Roffo[44]
1929 Jaulin and Grandclaude[45]
1929 Kleine[46]; 1, 2
1929 Volkmann[47]
1930 Diss[48]
1931 Abrikossoff[49]; 1, 2, 3, 4, 5, 6, 7
1931 Bolanos and Despaigne[50]
1931 Ceelen[51]; 1, 2, 3, 4
1931 Dawydow[52]
1931 Derman and Golbert[53]; 1, 2, 3
1932 Jorge, Nudelman, and Gringauz[54]; 1, 2, 3
1932 Meyer[11]; 1, 2, 3
1932 Schirmer[55]
1933 Glasunow[56]
1933 Roffo[57]
1934 Geschelin[58]
1934 Geschickter[59]†; 14 cases
1934 Kleinfeld[61]
1934 Klemperer[13]; 1, 2, 3, 4, 5, 6
1935 Gander[14]
1935 Kernan and Cracovaner[62]
1935 Martinez[63]
1935 Morpurgo[64]; 1, 2, 3
1935 Seiffert[65]
1935 Sjögren[66]
1936 Bobbio[67]
1936 Lattes[68]
1936 Parreira and Nunes de Almeida[69]; 1, 2
1937 Bang[70]
1937 Cappell and Montgomery[15]; 3, 4, 5, 6
1937 Gray and Gruenfeld[71]; 1, 2, 3, 4, 5
1937 von Szathmary[72]
1938 von Albertini[73]
1938 von Bahr[74]
1938 Ducuing, Ducuing, and Bassal[75]; 1, 2, 3, 4
1938 Frenckner[76]; 1, 2, 3, 4, 5
1939 Civatte and Ducourtioux[77]
1939 Dustin[78]
1939 Eickhoff[79]
1939 Fräsdorf[80]
1939 Geschickter and Maseritz[60]†
1939 Kramer[81]
1939 Leroux and Delarue[17]; 1, 2, 3
1941 Grayzel and Friedman[16]
1941 Holle[18]
1941 Kratochvil[82]
1941 Lascano-Gonzalez[83]; 1, 2
1941 Tamis and Kowles[84]
1941 Thoma[85]
1942 Bernier, Mann, and Ash[86,87]; 1, 2
1942 Iglauer[88]
1942 Monteiro[89]
1942 Ringertz[19]; 1, 2, 3, 4, 5, 6, 7
1942 Tuta and Schmidt[90]; 1, 2, 3, 4
1943 Altmann[91]; 1, 2, 3
1943 Ebert and Slepyan[92]
1943 Horn and Stout[20]; 27 cases
1944 Howe and Warren[22]; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
1944 Hartz[93]
1944 Lauche[21]; 1, 2, 3, 4, 5, 6, 7
1945 Crane and Tremblay[23]; 1, 2, 3, 4, 5
1945 Orr[94]
1945 Ravich, Stout, and Ravich[24]
1946 Ackerman and Phelps[25-26]
1946 Haagensen and Stout[95]; 1, 2, 3, 4, 5
1946 Powell[96]; 1, 2, 3, 4
1947 Khanolkar[34]; 1, 2, 3, 4, 6, 7, 8, 9, 10
1947 Simon[97]; 1, 2, 3, 4, 5, 6

* The following reports were studied and rejected: von Meyenburg,[28] Lino,[29] Loi,[30] Imperatori,[31] LaManna,[32] Muller,[33] Khanolkar[34] case 5, Cioni,[35] Cooper.[36] The following reports were not available to us: Jorge and Brachetto Brian,[37] Lepage,[38] Cheatle and Cutler.[39]

For data as to sex and age of patient, duration of disease and location, size and histologic type of lesion, see the thesis by one of us (G.H.M.)

† Apparently the cases reported by Geschickter[59] in 1934 and Geschickter and Maseritz[60] in 1939 are the same.

Course. There was no recurrence of the tumor on January 17, 1930, and on February 18, 1930, the child died of pleurisy and pneumonia after a short illness. No autopsy was performed, but there was no indication of metastasis.

Analysis of Cases

Deciding which cases reported in the literature could be accepted as true myoblastomas was a difficult task. In numerous instances these reports were not documented with photomicrographs or adequate descriptions and some, therefore, may have been included or excluded erroneously. This analysis is based on the 219 cases listed in Table I and the 10 new cases listed in Table II.

Table II

Summary of Data on 10 Mayo Clinic Cases of Myoblastoma Collected by Murphy, Dockerty, and Broders in 1947

Case	Sex	Age	Duration	Location	Size	Histologic type	Remarks
1	M	62		Tongue	0.5 cm.	Uniform	Epithelial hyperplasia
2	M	52	4 mos.	Tongue	1.3 cm.	Uniform	Epithelial hyperplasia; transitions
3	F	36	1+ wk.	Tongue	Small	Uniform	Epithelial hyperplasia
4	M	41	12 mos.	Tongue	0.7 x 0.5 cm.	Uniform	Epithelial hyperplasia
5	M	43	36 mos.	Tongue	2 x 3 cm.	Uniform	Epithelioma overlying; transitions
6	F	72		Labium	3.5 x 2.5 x 2.0 cm.	Uniform	
7	F	37	24 mos.	Skin, mastoid	2.5 cm.	Uniform	
8	M	50	54 mos.	Biceps	2.5 x 2.0 x 2.0 cm.	Pleomorphic	Mitotic figures
9	M	50	4 mos.	Hand	5+ cm.	Pleomorphic	Mitotic figures
10	F	12	5 mos.	Thigh	8 x 5 x 6 cm.	Pleomorphic	

Incidence. As noted above, 219 cases of myoblastoma were found in the literature up to October, 1947. Of the 10 cases encountered at the Mayo Clinic, in 9 the diagnosis was made during the years 1942 through 1947, showing that the entity, while still uncommon, should not be classed with the rarest tumors.

Site. Data as to site of tumor were available in all of the 229 cases (Table III), although accurate location was often difficult to ascertain.

For example, a tumor listed as occurring in the thigh might actually be of the skin, subcutaneous tissue, or muscle. This is not always the fault of the recording author, as it is frequently difficult to be sure of the actual tissue of origin. The tongue was by far the commonest site; it was the site in 78 cases (34.1 per cent). The skin was next, with 22 cases

TABLE III

Distribution of Lesions by Site in 229 Cases of Myoblastoma

Site	Cases	Per cent
Tongue	78	34.1
Skin	22	9.6
Breast	18	7.9
Subcutis	16	7.0
Maxilla	16	7.0
Muscle, excluding tongue	11	4.8
Vocal cord	8	3.5
Thigh	8	3.5
Lips	6	2.6
Buttocks	5	2.2
Mandible	4	1.7
Mouth, excluding tongue	4	1.7
External auditory canal	3	1.3
Trachea and bronchi	3	1.3
Vulva	3	1.3
Other sites*	24	10.5
Total	229	100.0

* Pharynx, arytenoid, axilla, hand, bladder, anus: 2 cases each. Occiput, orbit, lacrimal sac, middle ear, esophagus, urethral meatus, spermatic cord, pectoral region, back, loin, abdominal wall, heel: 1 case each.

(9.6 per cent), followed by the breast (7.9 per cent), subcutis, maxilla, and muscle in that order. As has been noted by others, there seems to be some predilection for the upper respiratory and digestive passages, which were the sites in 124 cases (54.1 per cent), including the 78 cases in which the tongue was the site.

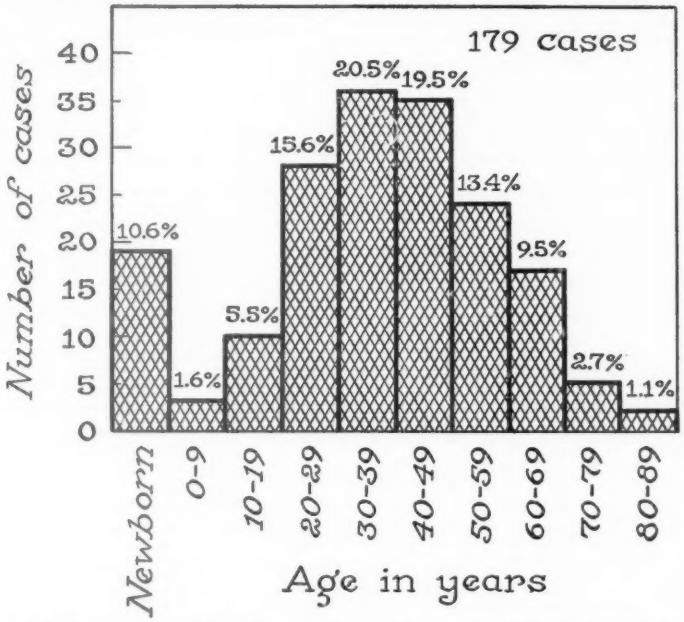
Age. Data on age were available in 179 cases (Text-Fig. 1). Apart from 19 "newborn" examples (congenital epulis type), myoblastomas were most numerous during the third, fourth and fifth decades, reaching a peak (20.5 per cent) during the fourth decade.

Sex. Sex had no apparent relation to incidence, type, or course of the tumor. In 183 cases in which data were available, 93 of the patients were male and 90 female.

Morphology. Grossly, the appearance of myoblastomas is not at all characteristic. In general, they appear as small lumps, often merely as raised and indurated patches as, for example, in the tongue. Occasionally, as when they occur beneath a mucous membrane, they may be pedunculated. They are small tumors, the great majority being between 0.5 and 2 cm. in diameter; the largest recorded was 27.5 cm. in diameter (buttocks[34]). The cut surface is usually homogeneous and

dull white to tan. Sometimes they may have a pseudocapsule owing to compression of the surrounding tissues, but microscopically they have no true capsule.

Histologically, myoblastomas fall into two main groups: uniform and pleomorphic. Abrikossoff[49] originally described four types but, as has



Text-Figure 1. Age distribution of patients who had myoblastoma (179 cases).

been pointed out by Cappell and Montgomery,[15] the distinguishing characteristics of these types are not constant. Thus most tumors described as Abrikossoff's types I, II, and III would seem to be better classified as "uniform" since they consist solely of the granular cells; his type IV, a mixture of spindle cells and a varying number of large granular cells, is covered by the term "pleomorphic." The terms "uniform" and "pleomorphic" were introduced by Howe and Warren[22] in 1944 but they classified their tumors according to Abrikossoff's types. In the 229 cases, 180 of the lesions can be classified as uniform, 13 as pleomorphic, and 36 as undetermined.

The *uniform* myoblastoma consists of sheets or cords of the large granular cells with a small amount of intercellular connective tissue. The granular cells, called myoblasts because of their resemblance to embryonic striated muscle cells, are large, round to oval with a poorly defined

cell membrane, granular and often acidophilic cytoplasm, and a single, central, vesicular nucleus. In some areas, these granular cells seem to fuse to form cylindric syncytial masses with several nuclei. The nucleoli vary considerably in size and are especially prominent in the malignant examples. The granularity of the cytoplasm also varies, being fine and evenly distributed in some, while in others the protoplasm is condensed into small, amorphous balls 3 to 4 μ in diameter. Staining of these cells for fat and mucus gives negative results but adequate studies on glycogen content have not been done since most or all of the tumors had been fixed in formalin. In myoblastomas found in striated muscle, transitions of adult striated muscle fibers to granular cells have been noted by many observers. In other sites, an arrangement of the granules in a manner suggestive of longitudinal and cross striations is occasionally seen. Frank cross striations are relatively rare and some observers[1,49,76] classify as rhabdomyoma any tumor in which they are present. Mitotic figures have been reported in the granular cells of the uniform type but they are quite unusual.[51,58]

The *pleomorphic* myoblastoma exhibits a very different histologic pattern, having in common only the granular cells, and even these are mostly quite unlike those found in the uniform type. There is a spindle cell stroma with scattered giant cells which are round, oval, strap or teardrop in shape, with a relatively large amount of granular cytoplasm and one or more central nuclei. These cells have a more distinct cell membrane and are seldom in close contact, being separated by spindle cells. The latter are often plump, have single nuclei, and sometimes show fine but distinct cross striations. Mitotic figures may be seen in both the large granular cells and the spindle cells. This pleomorphic type may grade almost imperceptibly into rhabdomyosarcoma and it is this type that has caused the greatest confusion in the literature. Howe and Warren[22] classified as rhabdomyoma or rhabdomyosarcoma any tumors of this type having "an appreciable number" of cells showing cross striations, while Cappell and Montgomery[15] similarly classified as such tumors those showing "any" cross striations.

A special subdivision of uniform myoblastomas has been described. Horn and Stout[20] noted an arrangement of the granular cells in the form of pseudo-alveoli that gave a picture reminiscent of tumors of endocrine origin. They expressed a belief that in Klemperer's[13] case 6 the lesion presented a similar picture, and Hartz[93] reported another example in 1944 (see also Powell's[96] case 3 and Khanolkar's[34] case 1, Table I). Horn and Stout applied the name "organoid" to myoblastomas

with this pattern but were unable to correlate the microscopic appearance with other distinctive findings.

As first noted by Heurtaux,[2] emphasized by Klemperer,[13] and since reported by numerous authors, hyperplasia of the overlying epithelium is a common finding in myoblastomas occurring beneath an epithelial surface. This has been especially common in tumors of the tongue where sometimes it has been so marked as to warrant the diagnosis of squamous cell carcinoma. Six cases of myoblastoma with overlying squamous cell carcinoma are reported in the literature[6,55,64,75,79,88] and in one of the new cases presented herein a similar picture obtained. In this connection it is interesting to note that in only 2 cases[1,21] has ulceration of this overlying epithelium been noted.

Clinical Course. Myoblastomas in general are slow-growing tumors and appear clinically as small, painless nodules that have been present for months or years. Frequently they are noticed accidentally by the patient or discovered in the course of routine physical examination. In the average case it is only the fear of cancer that brings the patient to the doctor. Clinically, for the most part, these tumors are benign and do not recur after local excision. Their greater clinical importance lies in the fact that they may be mistaken for some highly malignant neoplasm and unnecessary radical surgical treatment may be undertaken.

One special group of myoblastomas deserves at least passing mention. This is the so-called congenital epulis of the newborn found on the maxilla or mandible. Nineteen examples are reported in the literature and they are in all respects identical with the uniform myoblastoma found in the tongue and elsewhere.

Differential Diagnosis. The uniform myoblastoma must be distinguished from xanthoma, nevoxantho-endothelioma, chordoma, oncocytoma, and high-grade squamous cell carcinoma. The pleomorphic type may be confused with desmoid tumor, teratoma, mesodermal mixed tumor of the female genital tract, and giant cell tumor. The pleomorphic type grades into rhabdomyosarcoma from which it is distinguished, by definition, by the presence of an appreciable number of striated muscle cells in the latter.

Comment

New Cases. The 10 new cases reported herein are in all respects similar to those reported in the literature. In 7 the lesions were of the uniform type and in 3 they were pleomorphic. Age and sex were not remarkable. In 5 cases the lesions occurred in the tongue and were of the uniform type; all showed hyperplasia of the overlying epithelium,

and one lesion (case 5) included a low-grade squamous cell carcinoma. Stains for fat and for mucus gave negative results in all cases. Two tumors of the pleomorphic type recurred after apparently adequate excision and one of these showed a probable cerebral metastasis (case 8).

Histogenesis. Hypotheses as to the histogenesis of myoblastomas have followed two main lines of thought. The first is that these tumors are true neoplasms composed of the precursor cells of striated muscle arising either by a degeneration-regeneration process from adult muscle fibers or from heterotopic embryonic rests. The second hypothesis is that myoblastomas are not true neoplasms but rather are storage cell tumors composed of histiocytes or similar cells containing protein metabolites and are thus analogous to xanthomas.

The lesions in Abrikossoff's[1] first 5 reported cases, in 1926, were all situated in skeletal muscle and, on the basis of resemblance of the type cells to embryonic myoblasts as depicted by Godlewski[8] and the intimate relationship of these cells and striated muscle fibers in the histologic sections, he called the tumor a "Myoblastenmyome." Most later observers have endorsed this thesis. In the confirmatory evidence presented by these authors, a few points may be noted: (1) The tumor cells have a granular cytoplasm similar to that of early myoblasts. (2) An arrangement of the cytoplasmic granules in rows suggestive of young myofibrils has been noted. (3) Some of the granular cells have shown actual cross and longitudinal striations. (4) Numerous instances have been reported of apparent direct transition of the muscle fibers to granular cells. (5) Limiting membranes of the granular cells frequently are absent, giving the appearance of syncytial formation as in the normal histogenesis of striated muscle. (6) In myoblastomas of the tongue, the granular cells are found immediately beneath the surface epithelium where no muscle is ordinarily found; this supports the theory of neoplasia as against that of simple degeneration. (7) Further presumptive evidence of neoplasia is seen in the local invasiveness, lack of capsule formation, and recurrence of the tumor following apparently adequate excision.

Abrikossoff[1] expressed the belief that these tumor myoblasts arose from adult striated muscle fibers which had undergone a type of partial degeneration, probably initiated by trauma, and then regeneration with neoplasia of the regenerating cells. Diss[10] reached a similar conclusion independently and he and Abrikossoff were supported by later writers. But Klinge,[9] in 1928, reporting the first case of a myoblastoma in the skin, where no striated muscle is normally found, proposed a theory of origin from heterotopic rests of embryonic striated muscle cells. Abri-

kossoff,[49] reporting 7 more cases in 1931, was forced to accept Klinge's theory of origin for the myoblastomas arising where no striated muscle is normally found but retained his belief in a degeneration-regeneration process for those found in the skeletal musculature. Further support for Klinge's theory was given by the recognition of the so-called congenital epulis of the newborn as a typical myoblastoma; it seemed most probable that such a lesion must be of embryonic origin.

Most subsequent observers[98] followed Abrikossoff's explanation given in 1931, accepting both a dysontogenetic and a degeneration-regeneration origin. Montpellier[99] claimed that the adult type of striated muscle fibers often was present in "abnormal" locations—esophagus, prostate, urinary bladder—and that these tumors might arise from such aberrant fibers. Khanolkar[34] also felt it unnecessary to postulate embryonic rests since there were totipotent mesenchymal cells in the vicinity of small blood vessels throughout the body. The latter is not a new concept and in Maximow and Bloom's text[100] it is credited to Marchand.

A few, however, have raised definite objections. Thus Gander,[14] in 1935, expressed a belief that Diss' rhabdomyome granulo-cellulaire and Abrikossoff's Myoblastenmyome were different entities. The former, found only in the tongue, arose from adult striated muscle by an atypical disintegration while the latter might truly arise from myoblasts. In 1937, Gray and Gruenfeld[71] also raised a dissenting cry. After studying Godlewski's work on the histogenesis of muscle they could not agree with Abrikossoff as to the resemblance of the tumor cells to embryonic myoblasts; nor could they, in a study of animal and human embryos, find any cell forms similar to the type cell of the described tumors. They decided that the lingual myoblastomas did arise from striated muscle by a process of partial degeneration and that the cells were not young myoblasts, but that elsewhere the derivation was most uncertain and must be established in the individual case from a demonstrable relationship to parental cells; in this connection they suggested degenerated glandular epithelium as a possible source. Stout[20,101] was inclined to accept an origin from myoblasts but said that tissue cultures by Murray had not proved this conclusively.

In 1939, while reporting 3 new cases of myoblastoma, Leroux and Delarue[17] presented a new histogenetic hypothesis. The whole conception that the granular tumor cells were modified striated muscle elements was, they said, on a purely morphologic basis and hence could not be proved. They could not agree that these cells were myoblasts and they expressed the opinion that the transitional forms were artifact; there was the same apparent continuity with the cells of the overlying epi-

thelium. Nor could they see any proof that these tumors were true neoplasms. Accordingly, they proposed that the granular cells were mesenchymal cells of histiocytic type containing an unknown substance which might be glycogen. The tumor was formed by a local accumulation of these histiocytes as a manifestation of a general metabolic process.

Holle,[18] in 1941, arrived at conclusions similar to the above. He expressed the belief that the so-called myoblastomas were "Speicherzellgeschwülste," storage cell tumors, and that, on the basis of their staining reactions, the granular cells were mesenchymal cells which contained mucus. Ringertz,[19] in 1942, agreed that the so-called myoblastoma was a storage cell tumor but thought that the cells contained the products of protein breakdown rather than mucus. Lauche,[21] in 1944, agreed; staining of the granular cells for fat and mucin, in his experience, gave negative results and he expressed the belief that the granular material was of a protein nature. The tumor was, he said, analogous to a xanthoma.

At present it is not possible to make a definite decision as to the nature of the so-called myoblastomas. The storage tumor hypothesis awaits confirmation or condemnation by precise biochemical studies and cannot be excluded on purely morphologic grounds. Certain observations with reference to an origin from striated muscle cells can, however, be made at this time.

It would seem of primary importance to distinguish between the uniform and pleomorphic types. While these may be histogenetically related, they have different histologic and clinical characteristics, as previously noted. The uniform myoblastoma exhibits cells which are similar in appearance to the forms found in striated muscle that is regenerating after physical or physiologic trauma. Possibly there is a neoplasia of these regenerating muscle cells at their myoblastic or sarcoblastic stage; this is essentially Abrikossoff's contention.

The pleomorphic myoblastoma is unquestionably of myoblastic origin. The granular myoblasts of this lesion are similar to those seen in a teratoma of the ovary which contained both myoblasts and adult striated elements; they differ markedly from the type cells of the uniform myoblastoma. Also notable is the frequent association of granular cells and striated fibers in tumors of this type that have been called myoblastomas. The myoblasts of the pleomorphic type may arise from embryonic rests, but it is unnecessary to postulate rests when it seems so probable that there exists throughout the body primitive mesenchyme capable of differentiating into any type of adult connective tissue.[34,100] There is also the close relationship between the pleomorphic myoblastoma and rhabdomyoma and rhabdomyosarcoma. So close is this relationship that it is

arbitrary to separate them; it would seem more logical to consider the pleomorphic type as a low-grade rhabdomyosarcoma. This view is supported by Stout's[101] contention that striations are not necessary for the diagnosis of rhabdomyosarcoma.

Malignancy. The question of malignancy is somewhat confused by the previously noted uncertainty as to classification and diagnostic criteria. All of the cases of so-called malignant lesions reported prior to 1945[15,22,28,30,33,35,59,64,66] (15 cases, according to Howe and Warren[22]) were of pleomorphic type and, from their illustrations and descriptions, some of them should be classed as those of frank rhabdomyosarcoma. But Ravich, Stout, and Ravich[24] in 1945 and Ackerman and Phelps[25-26] in 1946 each reported one case of uniform myoblastoma with widespread metastasis. These cases seem to be instances of true malignant myoblastomas; in one the lesion originated in the urinary bladder and in one, in the gluteal region; both were classified as Abrikossoff's type III lesion. Khanolkar,[34] in 1947, reported 2 cases (cases 1 and 3, Table I) of apparently uniform myoblastoma with metastasis causing death. Most of the pleomorphic and a few of the uniform myoblastomas recurred after surgical removal, but this may well have been a result of inadequate excision due to the infiltrating nature of the tumor rather than an index of the relative malignancy of the cells.

In general, myoblastomas of uniform type are nearly all benign, although malignancy is possible, while those of pleomorphic type often exhibit at least a low-grade malignancy.

Therapy and Prognosis. Radiation therapy has been tried with little or no success[20,24,25,34]; surgical removal is the treatment of choice. For the benign uniform myoblastomas, local excision will effect a complete cure; this excision should be relatively wide, however, since the margin of these tumors is difficult to define. Until more is known about the entity, the rare malignant uniform myoblastoma must likewise be treated by simple excision unless the apparent malignancy of the tumor, as evidenced histologically, or its clinical spread demands more radical procedures. The pleomorphic myoblastomas should be treated as malignant neoplasms, with wide local excision being performed, and the patients should be watched closely for evidences of recurrence or metastasis. Definitely malignant pleomorphic myoblastomas behave in all respects like rhabdomyosarcomas, with as varied and uncertain a prognosis.

Summary and Conclusions

Myoblastoma was established as a tumor entity by Abrikossoff[1] in 1926. There have been numerous reports and reviews in the literature

since that time, from which we have compiled a list of 219 acceptable cases; we have reported 10 new cases, making a total of 229 cases on which our analysis is based.

Since classification on the basis of Abrikossoff's types[49] is unsatisfactory, the following classification is suggested: uniform type, benign or malignant; and pleomorphic type, benign or malignant.

The uniform myoblastoma arises from adult muscle fibers or from pluripotent mesenchyme, or it may possibly be a storage cell tumor analogous to xanthoma. It is rarely malignant and is usually cured by simple excision.

The pleomorphic type arises from pluripotent mesenchyme and is usually of low-grade malignancy; it often recurs after excision. This type is closely related to rhabdomyosarcoma and should probably be so designated.

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DESCRIPTION OF PLATES

PLATE 181

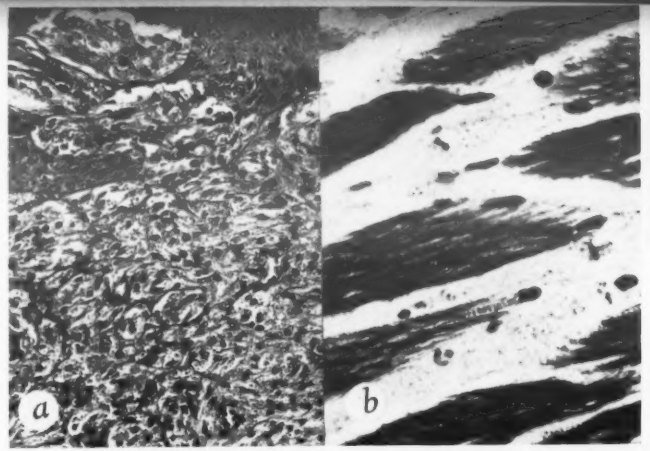
FIG. 1. Uniform myoblastoma. *a* (case 1). A mass of the granular cells is in close relation to the overlying hyperplastic epithelium. Hematoxylin and eosin stain. × 130. *b* (case 2). The intimate relationship of granular cells and striated muscle fibers at the periphery of the tumor is apparent. Bodian stain. × 365.

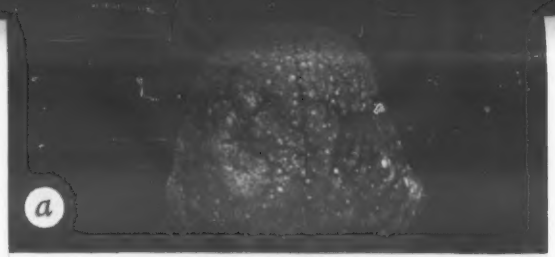
FIG. 2. Granular cells of the uniform myoblastoma. *a* (case 3). Fusion to form multinucleated syncytial masses is demonstrated. Bodian stain. × 365. *b* (case 4). Hyperplasia of the overlying epithelium. Hematoxylin and eosin stain. × 130.

FIG. 3 (case 5). Tongue (autopsy specimen). *a*. A raised, whitish, irregular patch of hyperplastic epithelium overlies a uniform myoblastoma on the left side of the dorsum. *b*. Infiltration and lack of encapsulation are evident. Mallory-Heidenhain stain. × 2½. *c*. The granular cells lie immediately beneath the squamous cell carcinoma. Hematoxylin and eosin stain. × 130. *d*. Transitional forms and intimate relationship of granular cells and striated muscle fibers are shown. Bodian stain. × 390.

XEROX

1





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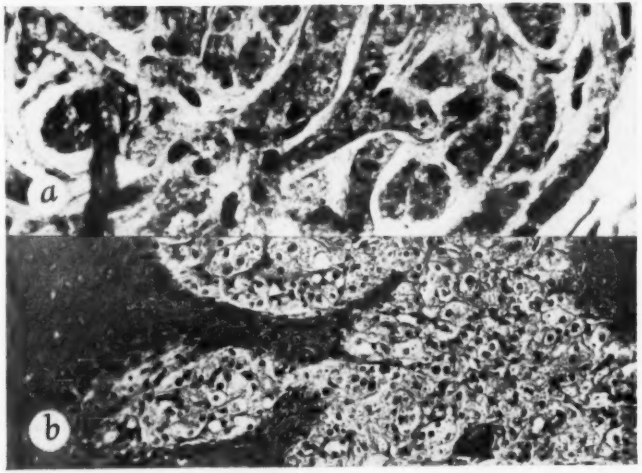


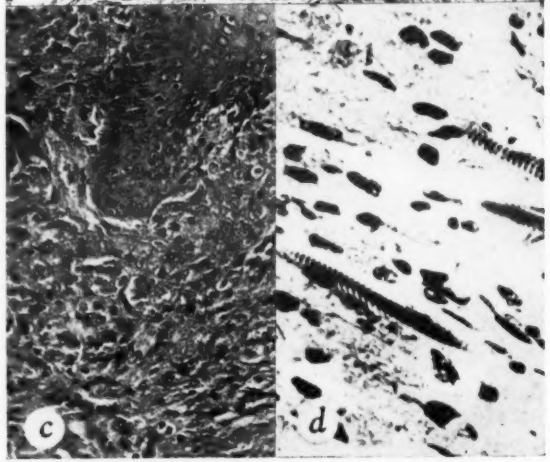


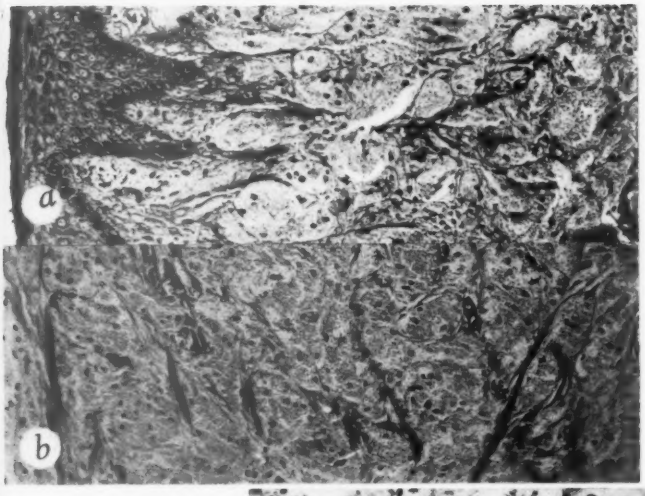
PLATE 182

FIG. 4. Uniform myoblastoma. *a* (case 6). Granular cells and overlying epithelium with hyperplasia and parakeratosis are demonstrated. Bodian stain. × 130. *b* (case 7). Granular cells are mingled with acellular connective tissue. Hematoxylin and eosin stain. × 130.

FIG. 5 (case 8). Pleomorphic myoblastoma. *a*. There are large myoblasts, some with coarsely granular and some with finely granular cytoplasm; many are multinucleated. Hematoxylin and eosin stain. × 130. *b*. An atypical mitotic figure is shown. Hematoxylin and eosin stain. × 435. *c*. Section from periphery showing a cylindrical granular cell mass with striated fibers in its substance. Bodian stain. × 830.

FIG. 6. Pleomorphic myoblastoma. *a* (case 9). Varied types of large cells with granular cytoplasm are shown. Many are round to oval and there are also elongated strap forms. Hematoxylin and eosin stain. × 130. *b* (case 10). A stroma of plump spindle cells is shown, with interspersed granular cells and a few multinucleated giant cells. Hematoxylin and eosin stain. × 130.

XEROX



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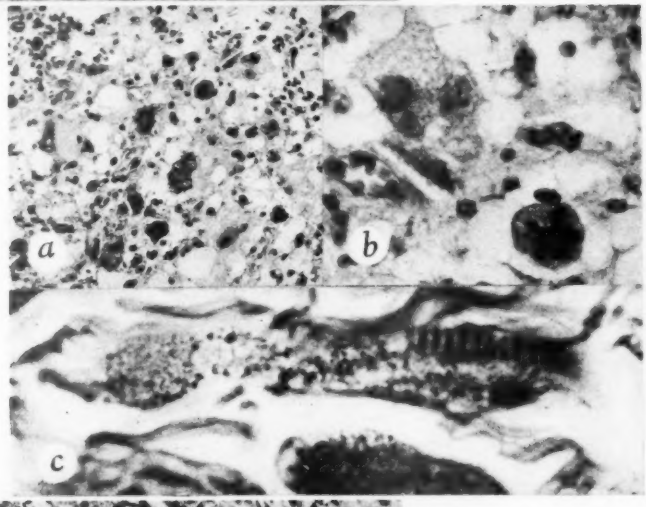

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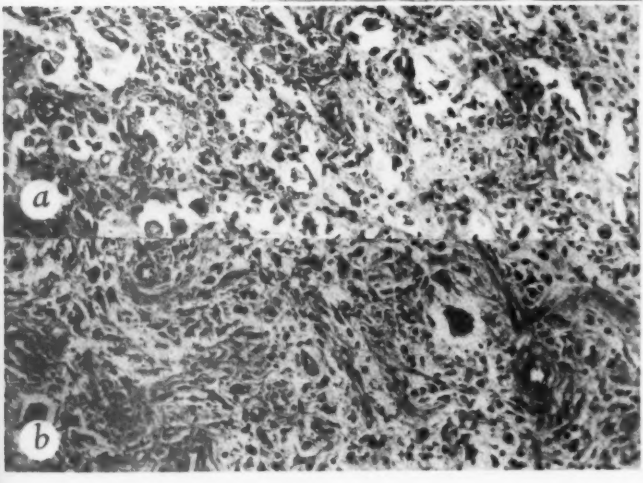

6

JUVENILE TUBERCULOUS INFECTION, POSSIBLY OF AVIAN TYPE*

WILLIAM H. FELDMAN, D.V.M., DOROTHY W. HUTCHINSON, M.D.,
VIRGINIA M. SCHWARTING, M.S., and ALFRED G. KARLSON, D.V.M.
(From the Division of Experimental Medicine, Mayo Foundation, Rochester, Minn., and Glen Lake Sanatorium, Oak Terrace, Minn.)

Definitely proved progressive tuberculous infections in human beings caused by tubercle bacilli of the avian type are exceedingly rare. The literature contains many alleged cases, but when examined critically few are convincing.† That the avian type of tubercle bacillus has seldom been proved responsible for progressive tuberculosis in man is of great interest when one appreciates that avian tuberculosis is an extremely common disease of poultry in large areas of the United States and throughout much of Western Europe. In addition, tuberculosis of swine, due to the avian type, is of common occurrence in areas where the disease occurs in chickens.

The character of the disease in its natural host—the chicken—is such as to provide favorable circumstances for its dissemination to susceptible animals. Its insidious course, its chronicity, the presence within the lesions of prodigious numbers of tubercle bacilli, and the tendency of the infection to produce ulcerative lesions of the intestine from which enormous numbers of the infective bacteria are discharged are important factors accounting for spread of the disease.

While much is known concerning the dissemination of avian tuberculosis to susceptible wild and domesticated animals, much uncertainty exists regarding its occurrence in human beings. Much of the confusion which exists is due to the fact that many alleged cases have been either inadequately described or incompletely or incorrectly studied. In spite of the skepticism that results from a critical examination of the data pertaining to the reported cases, one cannot ignore the fact that in exceptional circumstances avian tubercle bacilli have been the etiologic agent responsible for human infections. Such cases are extremely rare and the validity of their existence can be established only by careful studies using methods that will provide pertinent information regarding the pathogenicity of the acid-fast organisms isolated from the patient.

Typical avian tubercle bacilli are biologically unlike mammalian tubercle bacilli in several respects. The most important of these is their ability to produce, in susceptible hosts, progressive and frequently

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† The literature pertaining to infection of human beings by tubercle bacilli of avian type has been reviewed by Feldman[1,2] and by Rich.[3]

fulminating tuberculosis. Guinea-pigs, markedly susceptible to tubercle bacilli of the human and bovine types, usually resist even massive doses of avian tubercle bacilli given subcutaneously. When mycobacteria from human infections fail to produce progressive destructive tuberculosis in guinea-pigs, one should consider whether the organism is of an avirulent human or bovine type of tubercle bacillus such as may occur in lupus, or whether it is an avian tubercle bacillus, or an atypical strain which has not heretofore been identified. This information can be obtained only by properly conducted tests of pathogenicity.* When such tests are done properly, the identification of the avian tubercle bacillus may be said to rest on evidence that is valid and convincing.

Report of Case

The patient was a female child born on a Minnesota farm in December, 1944. She weighed 9 lbs. (about 4.1 kg.) at birth. The child was breast-fed for more than 15 months, after which she was allowed to choose her own diet. The family used raw milk from their own herd. The animals had reacted negatively to mammalian tuberculin when last examined 5 to 7 years previously.

The child developed normally, having none of the usual childhood diseases. No vaccinations or immunization inoculations had been done. Her one noticeable habit was frequent thumb sucking. She assisted her mother each day in gathering, cleaning, and crating eggs for market, and was particularly fond of playing with the chickens, which were allowed to roam at will about the farm during the summer and fall months.

At the age of 22 months symptoms suggestive of an acute upper respiratory infection occurred on October 4, 1946, and her condition had become alarming by October 10. A physician found the tonsils to be acutely inflamed and the symptoms to be suggestive of pneumonia. Penicillin was administered. The acute reaction subsided but attacks of fever, in which the temperature reached 104° F., and of dyspnea recurred repeatedly during the winter. Certain symptoms referable to the chest persisted and the child was admitted to a hospital in St. Cloud, Minnesota, for observation. Bronchoscopic examination did not reveal bronchial lesions or obstructions, but material swabbed from the bronchoscope was found on examination of smears to contain acid-fast bacillary forms.† A roentgenogram of the chest revealed massive involvement of the upper lobe of the left lung. A diagnosis of tuberculosis was made and the patient was transferred to the Glen Lake Sanatorium on April 29, 1947.

The mother, father, and 4 siblings (aged 10, 7, and 4 years, and 6 months) were examined for tuberculosis. The tuberculin reaction was negative on all except the mother. A subsequent roentgenogram of her chest did not show evidence of disease.

The child was not acutely ill at the time of admission to the sanatorium and has remained asymptomatic during residence. Her weight prior to the illness was 29 lbs. (about 13.2 kg.); her weight on admission was 29¾ lbs. (about 13.5 kg.). During hospitalization she gained 2½ lbs. (about 1.1 kg.). The rectal temperature remained between 98° and 100.2° F.

Examinations of blood made the day after the patient entered the sanatorium and approximately 9 months later failed to reveal any significant abnormalities of the

*The procedure for determination of the types of tubercle bacilli has been described previously.[4]

†Bronchoscopic examination was performed by Dr. E. N. Milhauft, St. Cloud, Minn.

hemoglobin or cells. On admission the blood sedimentation rate as determined by the method of Westergren was 16 mm. in 1 hour at 25° C. Nine months later the rate was 12 mm. in 1 hour at 24° C. Specimens of urine contained an increased number of leukocytes with occasional clumps, erythrocytes, and a trace of albumin. A series of cultures of urine were negative for acid-fast bacilli.

A roentgenogram of the chest on April 30, 1947, revealed marked density throughout the left upper lobe with no evident change on comparison with those taken on April 8 and April 25. The patient was tested with tuberculins on four different occasions. With the exception of the first test, both P.P.D. (purified protein derivative) and avian tuberculin were used. The results are summarized in Table I.

TABLE I

Results of Intradermal Injections of P.P.D. and of Avian Tuberculin

Date	Tuberculin	Reaction*
May 5, 1947	P.P.D., 0.00002 mg.	18 by 16 mm. erythema 12 by 11 mm. induration
October 20, 1947	P.P.D., 0.00002 mg.	15 by 14 mm. erythema 13 by 10 mm. induration
	Avian tuberculin, 0.1 cc. of 1:10,000 dilution	17 by 16 mm. erythema 13 by 11 mm. induration
February 2, 1948†	P.P.D., 0.00002 mg.	18 by 17 mm. erythema 8 by 7 mm. induration
	Avian tuberculin, 0.1 cc. of 1:10,000 dilution	46 by 33 mm. erythema 27 by 25 mm. induration
May 10, 1948†	P.P.D., 0.00002 mg.	9 by 8 mm. erythema 5 by 5 mm. induration
	Avian tuberculin, 0.1 cc. of 1:10,000 dilution	28 by 22 mm. erythema 20 by 18 mm. induration

* Recorded 48 hours after injection.

† Reactions on these dates were markedly dissimilar. The reaction to avian tuberculin was a firm, well circumscribed induration; the reaction to P.P.D. was soft, pale, and poorly outlined. The reactions to avian tuberculin persisted for several days longer than the reactions to P.P.D.

Gastric contents were collected on April 30, 1947, the day after the patient's admission to the sanatorium. Stained smears of the gastric washing were negative for acid-fast bacilli. From the portion of the material used for making cultures one colony appeared. This colony was atypical in appearance for human tubercle bacilli, but since it consisted of acid-fast bacilli a portion was used to inoculate a guinea-pig. Results of this inoculation will be referred to later in this report. Gastric contents collected on two occasions in June, 1947, and again in September and in October of the same year all failed to yield acid-fast organisms. An additional gastric lavage specimen was obtained in May, 1948. From a portion of this material attempts were made to isolate acid-fast bacilli and a portion was used to inoculate one rabbit. The results failed to reveal the presence of tubercle bacilli.*

Since the patient was hospitalized, there has been a rapid progressive improvement of the pulmonary lesion as shown by successive roentgenograms of the chest (Figs. 1a and b). The appearance of the lesion on admission and the subsequent changes do not differ significantly from the primary tuberculous involvement found in roentgenograms of children infected by tubercle bacilli of the human type except for the absence of demonstrable calcification, which not infrequently becomes evident within

* These procedures were done at Glen Lake Sanatorium, Oak Terrace, Minn.

a year after the onset of the disease. The patient's tonsils were still markedly enlarged when this paper was written.*

Clinical Bacteriologic Observations

The culture obtained from the gastric lavage specimen appeared on Petragnani's medium after 21 days of incubation. It consisted of one small colony, which had a buff color, was smooth, entire, and of a soft or pasty consistency. Considered physically unlike typical *Mycobacterium tuberculosis hominis,* the culture was tested for pathogenicity by injecting one guinea-pig intraperitoneally. When the animal died 39 days later, the spleen was enlarged but without grossly visible lesions. The liver contained one raised, buff-colored lesion. One substernal abscess was noted. Ascites and hydrothorax were recorded also. A smear preparation from the substernal abscess revealed many acid-fast bacilli. From the substernal abscess and from the spleen of the guinea-pig, cultures of acid-fast bacilli were recovered. The organism grew luxuriantly and produced a soft, smooth, unctuous growth that was similar in appearance to the original colony obtained from the gastric lavage specimen.

Histopathologic examination of the spleen of the guinea-pig inoculated with the culture from the gastric lavage specimen revealed a widely disseminated tuberculous process with numerous small tubercles situated largely in the pulp spaces. Acid-fast bacilli, while present, were few. The liver, likewise, contained similar small tubercles in addition to the larger subcapsular lesion. The latter was characterized by a necrotic central portion and a broad peripheral zone of epithelioid cells. Acid-fast bacillary forms were exceedingly numerous in the cellular débris in the center of the nodule.

After the first gastric specimen had yielded acid-fast bacilli, several additional gastric lavage specimens were examined but no additional acid-fast bacilli could be demonstrated either by culture or by animal inoculation. A summary of the attempts to demonstrate tubercle bacilli in the gastric lavage specimens is given in Table II.

The cultural characteristics of the organism obtained by gastric lavage were dissimilar in many important respects from those of tubercle bacilli of the human type. The former grew more rapidly, usually producing a luxuriant growth in 12 to 14 days. Instead of a dry, wrinkled, crumbly growth like that of the human type, cultures from the patient produced a diffuse spreading growth with discrete hemispheric colonies in the midst of the main surface growth.

* Tonsillectomy was done on February 22, 1949, by Dr. C. R. Myre, Paynesville, Minn. It was not possible to demonstrate tubercle bacilli in the tonsils by appropriate animal inoculation or cultural procedures. Histopathologic examination revealed no acid-fast rods nor any lesions resembling tuberculosis.

The miscibility of the bacteria in distilled water was high. A uniformly turbid suspension of the bacterial cells could be obtained without diffi-

TABLE II

Summary of Attempts to Demonstrate Tubercle Bacilli by Culture or by Animal Inoculation in Gastric Lavage Materials Collected on Six Different Occasions

Specimen	Date	Procedure	Results
1	4–30–47	Culture	One colony of acid-fast bacilli
		Guinea-pig	Died in 39 days; tuberculous lesions of liver and spleen
2	6–11–47	Culture	Negative
3	6–14–47	Culture	Negative
4	9–26–47	Respective specimens injected on date collected into the same 2 animals, 1 guinea-pig, and 1 rabbit	Negative for tuberculosis at necropsy; cultures from spleens of both animals negative for tubercle bacilli
5	9–29–47		
6	10–3–47		
7	5–19–48	Culture	Negative
8	5–20–48	Culture	Negative
		Rabbit	Negative

culty, whereas with the usual cultures of tubercle bacilli of human type it is not easy to obtain an even suspension, clumps being eliminated with difficulty.

The growth studied had a soft, moist, and somewhat creamy consistency. It was whitish gray and had a glistening appearance by reflected light.

In liquid mediums, such as Proskauer and Beck's* to which blood serum had been added, growth was rapid and diffuse.

The sensitivity of the culture to streptomycin *in vitro* was determined. It was found that growth was inhibited in the presence of 10 μg. of streptomycin per cc. of medium but not by 5 μg. This observation is perhaps of some significance, since practically all strains of tubercle bacilli of human type, isolated from patients who have not been treated with streptomycin, have sensitivity *in vitro* to less than 1 μg. of streptomycin per cc. Conversely, the several strains of avian tubercle bacilli that we have studied have been resistant *in vitro* to at least 5 μg. of streptomycin per cc.

The clinical and laboratory findings indicated definitely that the patient had tuberculosis but the physical properties of the one culture obtained and the atypical character of the disease produced in the guinea-pig created uncertainty as to the true character of the myco-

*Proskauer, B., and Beck, M. Beiträge zur Ernährungsphysiologie des Tuberkelbacillus. *Ztschr. f. Hyg. u. Infectionskrankh., Leipz.*, 1894, 18, 128–152.

bacterium isolated. Consequently, additional studies were undertaken to "type" the organism by the tests of pathogenicity.*

Experimental Observations

Tests of Virulence. The inocula used for determination of the type of the infective mycobacteria were the original culture obtained from the first gastric lavage specimen and the culture recovered from the spleen of the one guinea-pig. In addition, a suspension prepared by pooling splenic materials obtained from 2 rabbits that died after inoculation with the culture recovered from the spleen of the guinea-pig was used to inject guinea-pigs, rabbits, and chickens. Four separate experiments to determine virulence were done. Pathogenicity of the bacterial culture for guinea-pigs, rabbits, and chickens was determined.† The guinea-pigs were inoculated subcutaneously, the rabbits and chickens intravenously.

The results of the tests of virulence, summarized in Table III, provide convincing evidence that the acid-fast organisms constituting the respective inocula were avian type tubercle bacilli. The lethal potentialities for rabbits and chickens were demonstrated repeatedly in an impressive manner while portions of the same inocula were essentially nonpathogenic for guinea-pigs, which were kept under observation for from 3 months to more than 4 months after being inoculated.

The fact that the one guinea-pig inoculated with a portion of the original culture obtained from the first gastric lavage specimen died presumably of tuberculosis justifies brief comment. While it is generally true that guinea-pigs have a high resistance to avian tubercle bacilli, occasionally an animal may be encountered that is markedly susceptible.‡ When this occurs, it is necessary to restudy the virulence of the infective agent by the inoculation of additional guinea-pigs. Generally speaking, mycobacteria that produce progressive and eventually severe tuberculous disease in chickens and rabbits are not capable of producing well marked or generalized tuberculosis in guinea-pigs. This is the essential difference that distinguishes avian tubercle bacilli from the human and bovine types when tests of virulence are utilized for typing.

Subsequent observations are adequate to establish that the development of tuberculosis in the one guinea-pig inoculated with the original gastric culture took place because of the unusually low resistance of this

* Studies to determine the bacillary type of the organism obtained from the gastric lavage specimens were done in the Division of Experimental Medicine, Mayo Foundation, Rochester, Minn.

† Before being inoculated, all chickens were tested with tuberculin and failed to react.

‡ A comprehensive review of the susceptibility of guinea-pigs to avian tubercle bacilli has been published previously.[1]

Results of Tests of Pathogenicity of Acid-fast Bacteria Isolated from Gastric Lavage Specimen and of Culture Obtained from Spleen of Guinea-Pig that Died 30 Days After Inoculation with Culture Obtained from First Gastric Lavage

Severity of tuberculosis*

Results of Tests of Pathogenicity of Acid-fast Bacteria Isolated from Gastric Lavage Specimen and of Culture Obtained from Spleen of Guinea-Pig that Died 39 Days After Inoculation with Culture Obtained from First Gastric Lavage

Experiment	Inoculation materials	Animal	Days before death	Severity of tuberculosis*			Tubercle bacilli recovered
				Spleen	Liver	Lungs	
1	Original culture from gastric lavage	Guinea-pig 1	111 (killed)	No lesions	No lesions	No lesions	From spleen
		Guinea-pig 2	111 (killed)	No lesions	No lesions	No lesions	No growth from spleen
		Rabbit 1	5 (failure)	No lesions	No lesions	No lesions	No attempt
		Rabbit 2	24	++++	++++	++	From spleen
2	Culture from spleen of guinea-pig inoculated with culture from gastric lavage	Guinea-pig 3	6 (failure)	No lesions	No lesions	No lesions	No attempt
		Guinea-pig 4	12 (failure)	No lesions	No lesions	No lesions	No attempt
		Rabbit 3	17	++++	++++	+	From spleen
		Rabbit 4	17	++++	+++	+	From spleen
3	Pooled splenic suspensions of rabbits 3 and 4	Guinea-pig 5	92 (killed)	No lesions	No lesions	No lesions	No attempt
		Guinea-pig 6	92 (killed)	No lesions	No lesions	No lesions	No growth from spleen
		Rabbit 5	24	++++	+++	++	From spleen
		Rabbit 6	29	++++	+++	+++	From spleen
		Chicken 1	61	++++	+++	+	From spleen
		Chicken 2	74	++++	++++	+	From spleen
4	Transplant of culture from gastric lavage (5 months after experiments 1 and 2)	Guinea-pig 7	130 (killed)	No lesions	No lesions	No lesions	No attempt
		Guinea-pig 8	130 (killed)	No lesions	No lesions	No lesions	No attempt
		Rabbit 7	7 (failure)	No lesions	No lesions	No lesions	From spleen
		Rabbit 8	21	++	++++	+	From spleen
		Chicken 3	33	++++	++++	No lesions	From spleen
		Chicken 4	33	++++	++++	No lesions	From spleen
		Chicken 5	32	++++	++++	No lesions	From spleen

* Based on histopathologic examination of the tissues. Severity of infection graded 1 plus to 4 plus.

particular animal to avian tubercle bacilli. Reference to Table III shows that in 4 additional guinea-pigs inoculated subsequently with the same culture, tuberculosis failed to develop; yet portions of the same inoculum proved highly virulent for rabbits and for chickens.

Sensitivity to Tuberculin. All of the animals used in the typing experiments were tested with avian tuberculin and with mammalian tuberculin injected intracutaneously. Standard avian tuberculin supplied by the Bureau of Animal Industry of the United States Department of Agriculture was used. The mammalian tuberculin used was O.T. diluted 1:10. The respective dose for each tuberculin was 0.1 to 0.2 cc. All animals without exception reacted definitely and often dramatically to avian tuberculin while the reactions to mammalian tuberculin were negative or indefinite.

Possible Source of Infection

After the avian character of the culture obtained from the gastric lavage specimen had been established, a survey was made to determine the possible source of the patient's infection. A visit to the child's home revealed the usual domesticated farm animals including chickens, swine, and cattle. Arrangements were made to have all animals on the premises tested with avian tuberculin and with mammalian tuberculin.* The results are summarized in Table IV.

Table IV

Tuberculin Tests of Farm Animals

Species	Number tested	Tuberculin sensitivity	
		Avian	Mammalian
Chickens	430	217 (50 per cent)	2* (0.5 per cent)
Swine	6	2 (33 per cent)	None
Cattle	33	10 (30 per cent)	None

* The same birds were also sensitive to avian tuberculin.

It can be noted that a large population of chickens was maintained on the premises and that approximately 50 per cent gave a positive reaction to avian tuberculin. (Subsequently 13 of the chickens that reacted to tuberculin were killed for necropsy and tuberculous lesions were demonstrated grossly in 11.) The fact that except during the winter months the chickens were not confined but roamed at will over the barnyard

* The tuberculin tests were conducted by Dr. M. R. Zinober of the United States Department of Agriculture.

probably accounts for the sensitivity to avian tuberculin of 2 of the 6 swine and 10 of the 33 cattle.

The evidence obtained from this phase of the study indicated that a considerable reservoir of potential infection existed and that dissemination of the infection to heterogeneous species had taken place. That the patient associated with the chickens during playtime and assisted in cleaning and crating eggs for market provided further opportunity for exposure to the infective agent. The patient was a "thumb sucker" and this also should be considered in explaining the transmission of the infective agent. The facts definitely indicate that there existed in the child's environment sufficient opportunity for a susceptible host to become infected with the organism of avian tuberculosis.

Comment

In evaluating the evidence that accumulated in the study of this case one may summarize first those facts in support of the patient's being infected with *Myco. tuberculosis avium*. The patient did have tuberculosis. This was established clinically and bacteriologically. Every effort failed to incriminate the human or the bovine type of the tubercle bacilli. While there was no known source for infection with the mammalian type of the organism, there did exist ample opportunity for infection with the organism of avian tuberculosis.

The patient was equally or more sensitive to avian tuberculin than she was to mammalian (P.P.D.) tuberculin. The marked sensitivity to avian tuberculin is of uncertain significance, since it is well known that there exists a certain reciprocal relationship between the tuberculin sensitivity produced by avian and by mammalian types of tubercle bacilli. However, it is generally true that a more pronounced reaction is elicited by homologous than by heterologous tuberculins. In other words, there is a relative specificity to the sensitivity produced by avian and by mammalian tubercle bacilli, respectively, but a certain overlapping may be expected in some species. Considered alone, the sensitivity of human beings to avian tuberculin is certainly insufficient to establish a diagnosis of infection with avian tubercle bacilli. However, a definitely positive reaction to avian tuberculin equal or superior to the reaction to mammalian tuberculin is perhaps of some significance, especially when considered along with other and more direct evidence such as the isolation of avian tubercle bacilli from clinical material.

Another fact in support of the thesis that the patient's tuberculosis was due to the avian type of tubercle bacilli is that the culture was ob-

tained by gastric lavage 3 weeks after she had been removed from the infective environment. The period of separation from the premises where avian tuberculosis was rampant should preclude the likelihood that the tubercle bacilli obtained from the patient might have been ingested a few hours previously and represented an incidental finding.

It is also important that in the laboratory where the isolation of the organism was accomplished there was an absence of known cultures of the avian variety of tubercle bacilli.* Therefore the occurrence of this particular culture cannot be explained by an inadvertency.

Lastly, and of most importance in support of a diagnosis of infection due to the bacillus of avian tuberculosis, is the fact that the culture of acid-fast bacilli obtained from the gastric lavage specimen was proved by adequate tests of pathogenicity to be *Myco. tuberculosis avium*. Thus we have a case, clinically and roentgenographically considered to be tuberculosis, from which was obtained from a gastric lavage specimen a culture of acid-fast bacilli. The physical appearance and pathogenesis of this organism were unlike those of either human or bovine tubercle bacilli. Instead, the organism had all the essential physical characteristics of the bacillus of avian tuberculosis and was established as such by numerous tests of pathogenicity.

Since progressive infections due to avian tubercle bacilli are extremely rare in human beings, the evidence must be considered objectively and skepticism voiced if justified. Although the evidence, as set forth in previous paragraphs, impressively supports the conclusion that the patient studied had a severe progressive pulmonary infection due to the avian variety of tubercle bacilli, a basis for skepticism does exist.

If the patient did in fact receive her tuberculous infection from the environment of the farm premises, it should be noted that the other children in the family did not become infected. Can this be explained on the basis that the patient had a greater opportunity to become infected through more frequent and intimate contact or on the basis of a peculiar intrinsic susceptibility? The true explanation must remain obscure.

Another fact that justifies skepticism concerns the failure to obtain more than one positive culture from the patient. It will be recalled that only a single colony of acid-fast bacteria was obtained. In animal infections due to avian tubercle bacilli the organisms are usually exceedingly numerous and can be cultured readily. In this instance, although several subsequent attempts were made to culture tubercle bacilli from gastric lavage specimens, the second attempt was not made

* The organism was isolated in the bacteriologic laboratory of Glen Lake Sanatorium.

until 42 days had elapsed. During this interval the patient had been kept on strict sanatorium regimen. Perhaps the progress of the disease had ceased and regression had begun. If healing and resolution did commence during this period, an influence on the number of tubercle bacilli finding egress from the diseased lung might be expected.

Lastly, the fact that the original culture proved virulent for the one guinea-pig inoculated was indeed unusual. This can be dismissed by again pointing out that an occasional guinea-pig has an exceedingly low resistance to avian tubercle bacilli. In this instance subsequent studies of the culture established the fact that it was essentially nonpathogenic for guinea-pigs.

Considering all of the evidence one may conclude that (1) the patient did have tuberculosis and (2) the causative organism was probably *Myco. tuberculosis avium*. However, the evidence necessary for the absolute proof of the etiologic relationship of this variety of the tubercle bacillus to the patient's illness was not obtained. Perhaps subsequent observations of the patient may provide data that will justify more definite conclusions.

Summary

A study was made of a culture of acid-fast bacilli from a gastric lavage specimen obtained from a female child approximately 2½ years of age. Roentgenographically the lungs showed extensive involvement of the left upper lobe diagnosed as tuberculosis. The child had lived on a Minnesota farm on which tuberculosis among the chickens was rampant. The child played with the chickens, handled eggs, and was a "thumb sucker." Extensive studies of the culture obtained revealed that the physical characteristics and pathogenic behavior of the culture were similar in every respect to those of *Mycobacterium tuberculosis avium*. While the causative relationship of the bacterium to the pathogenesis of the pulmonary disease could not be proved definitely, the evidence strongly indicates such a relationship. The study illustrates the difficulties of proving unequivocally the etiologic relationship of *Myco. tuberculosis avium* to tuberculous infections in human beings.

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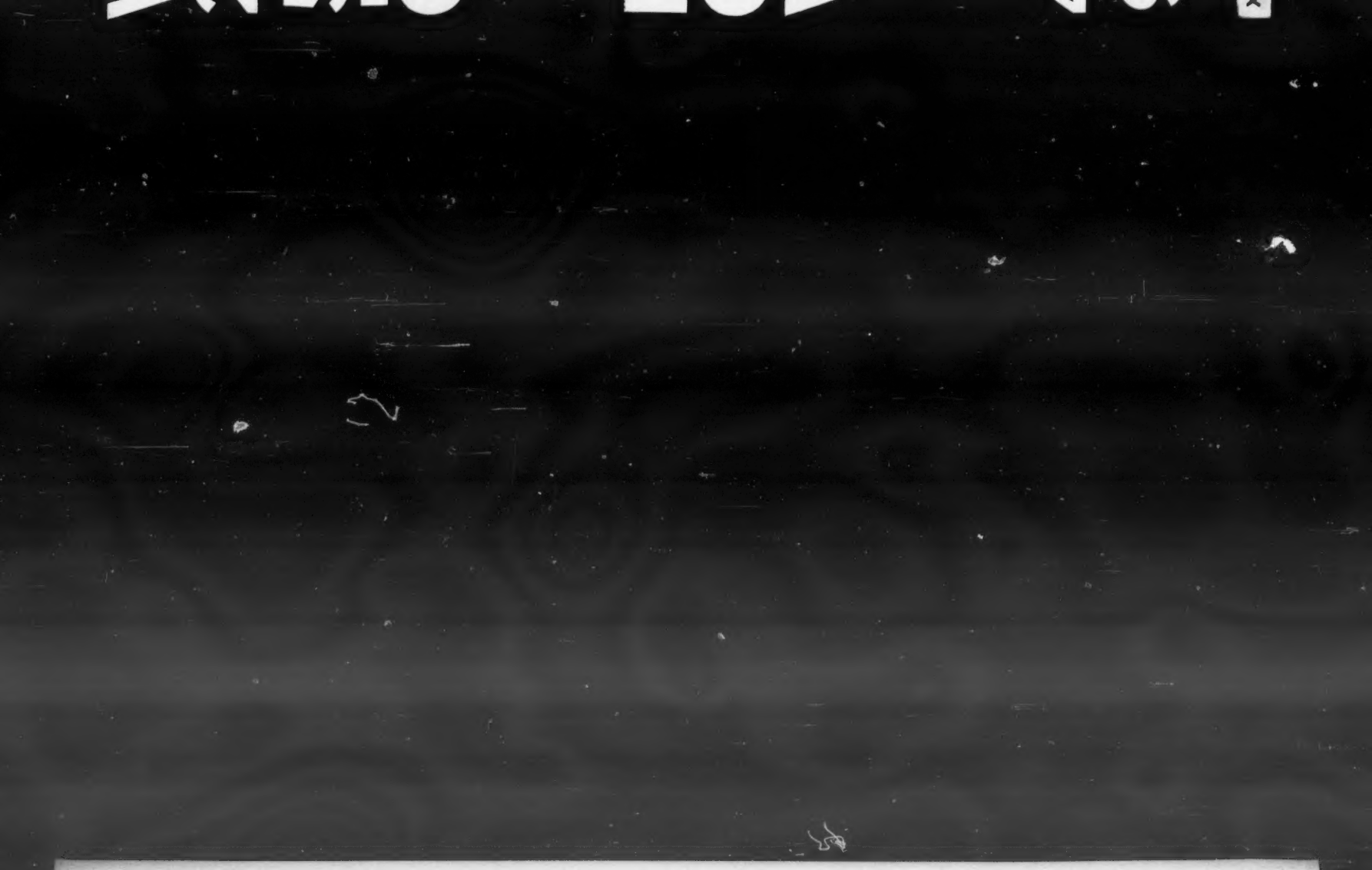
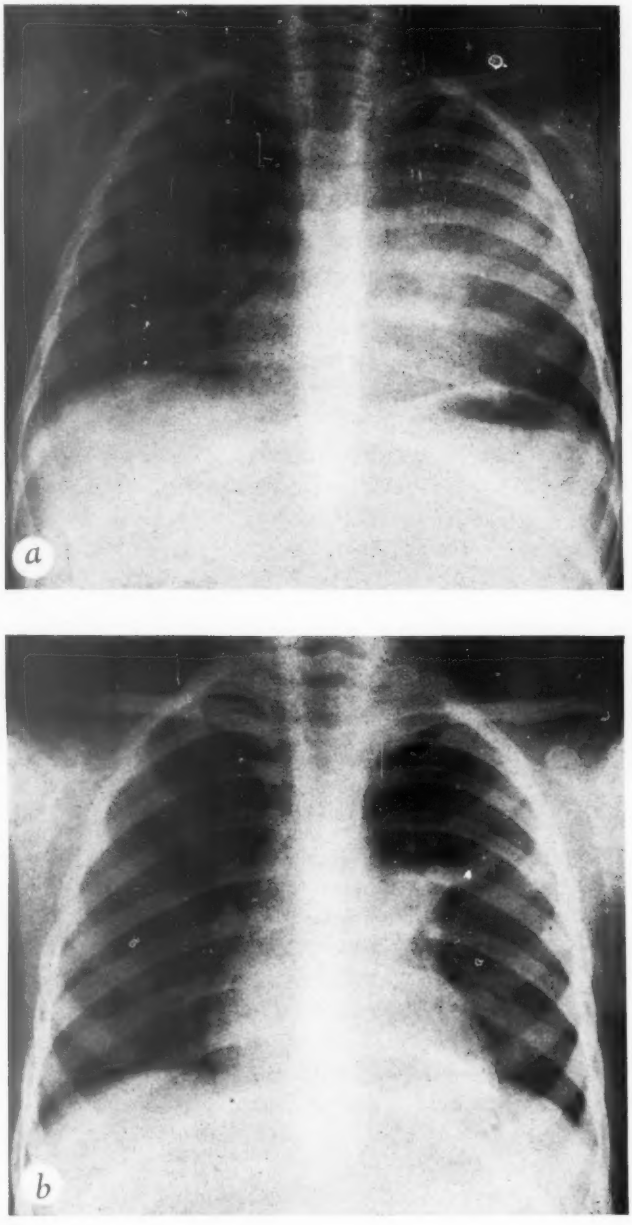
DESCRIPTION OF PLATE

PLATE 183

FIG. 1*a*. Chest of patient at time of admission to sanatorium. There is extensive infiltration of the left lung. *b*. Chest of patient 9 months later. Marked improvement in the appearance of the left lung is evident.





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Feldman, Hutchinson, Schwarting, and Karlson Avian Tuberculosis in a Child

LYMPHOID TISSUE AND ITS RELATION TO SO-CALLED NORMAL LYMPHOID FOCI AND TO LYMPHOMATOSIS

I. Qualitative Study of Lymphoid Areas in the Pancreas of Chickens*

Alfred M. Lucas, Ph.D.

(From the U.S. Regional Poultry Research Laboratory,† East Lansing, Mich.)

Birds, generally, are known to possess numerous, widely scattered accumulations of lymphoid tissues in various organs. Danchakoff[1] and Mjassojedoff[2] in their studies on hematopoiesis regarded these structures as normal to the bird. They are said to correspond to the lymph nodes of mammals.[3,4] Nonidez[5] described the development of eosinophils in the region of the gonad. Jordan[6] has described granulopoietic transformation of cells from lymphoid nodes located in the bone marrow, liver, and other organs of birds. The fact that accumulations of lymphocytes do show potentialities of development into cells of other types may not be adequate evidence that the region where they are found should normally have lymphoid tissue. The term "normal" is used here in the sense that normal structures arise as a part of the ontogenetic processes of the bird in anticipation of future needs. Examples of lymphoid structures which may be regarded as normal are the thymus, bursa of Fabricius, and spleen. If the lymphoid tissue in parenchymal organs has developed in response to external agents, it is called abnormal in this study. The term "abnormal" in no wise precludes the possibility that these lymphoid areas may be valuable to the general well-being of the host in defense against foreign external agents, and that they may not serve hematopoietic functions. The terms have been used to simplify the discussion of the problem. It should be added that a descriptive embryologic study alone will not give us the answer in view of the numerous suggestions made in the literature that the agent of lymphomatosis, as well as certain bacteria, is transmitted through the egg.[7-9]

Lymphomatosis is a disease involving the lymphoid tissue of the body and in many cases the lesions are found in the same organs which contain the lymphoid foci, the normality of which is being questioned. Numerous publications have described the clinical symptoms and pathologic alterations which seem to be involved in the avian leukosis complex.[7,10-14] Lymphomatosis is one aspect of the complex, and in the material involved in this series of papers is represented by the ocular, neural, visceral, and osteopetrotic forms.

* Received for publication, September 7, 1948.

† United States Department of Agriculture, Agricultural Research Administration, Bureau of Animal Industry.

A criterion for diagnosis of this disease is the presence of grossly visible tumors at necropsy. The tumors among different individuals vary in size from a barely perceptible swelling on a single nerve or organ to large, overgrown, multiple tumors. It is conceivable that large, proliferating tumors may be a direct cause of death but it is hard to believe that a barely visible tumor which apparently does not interfere with a vital function can be the immediate and direct cause of death. According to Doyle,[10] "The pathology of this disease . . . strongly suggests that it is infectious in nature." If lymphomatosis is an infectious disease, then its causative agent may well produce systemic effects on the organism in addition to stimulative effects on lymphoid tissue. The latter under suitable conditions may produce a neoplastic, transplantable tumor as an end result.

The purposes of this series of papers are to present qualitative and quantitative evidence which can be brought to bear on the problems of normality of ectopic lymphoid foci, to determine the significance of these lymphoid reactions in relation to lymphomatosis and, finally, to give some suggestions concerning the microscopic diagnosis of the disease. The present paper deals with descriptive aspects of the problem.

The pancreas rather than the liver was chosen for the initial studies for several reasons: (1) The lymphoid areas are usually sufficiently focal to be easily measured; (2) the pancreas is not considered a normal hematopoietic organ, either in birds or in mammals; (3) its slender shape and uniformity of internal organization facilitate the taking of comparable sections; and (4) the same slides can be used for a comparison between intranuclear inclusions present in the islands of Langerhans and the lymphoid tissue. Later studies will be extended to other species and other organs.

It goes without saying that an adequate diagnosis of the bird as a whole cannot be made on one section. The pancreas is merely one of a group of organs and tissues which might be chosen for study. However, by intensive study of one organ it should be possible to elucidate basic principles involved in lymphoid reactions, which should be applicable to all parts of the body.

Materials and Methods

Survivors of one year's population used in the breeding program of the Laboratory formed the material for this study. The birds were killed at an average age of slightly over 600 days. All were Single-Comb White Leghorn females. The original population was composed of 1123 birds divided among 14 inbred lines and an F_1 cross of two of these lines (9×10).

The incidence of grossly visible lymphoid tumors found at necropsy has been used as a measure of resistance and susceptibility. On this basis the inbred lines and cross varied from 7.5 to 77 per cent in incidence of lymphomatosis based on the original population, or from 9 to 100 per cent when the population was corrected for deaths not associated with gross tumors.

Tissues were taken from 319 of the 352 survivors of the population and from all 14 of the surviving birds which were diagnosed as grossly positive for lymphomatosis. As to the anatomic type, of these 14, 4 were neural, 8 were visceral, 1 neural and visceral, and 1 ocular. In no case was the pancreas diagnosed as positive for lymphoid tumor on gross examination. Diagnoses based on gross lesions were taken from the necropsy records compiled by the Laboratory veterinarians.

A portion of pancreas about 13 to 19 mm. long was removed from approximately the center of the organ and fixed in Petrunkevitch no. 2.[20] All sections were cut at 5 μ and stained with Galigher's hematoxylin and triosin.[15]

The data on areas of the total section and of lymphoid tissue were obtained by tracing the projected images with a planimeter and converting the reading to square millimeters. When projecting the sections, large vessels and ducts were excluded from the drawing so that values obtained were a measure only of parenchymal tissue and small vessels and ducts. The entire section was searched for lymphoid areas but only those were measured which were located below the serosal connective tissue. Thus those which formed part of the pancreatic omentum or lay at tips of lobes were not included.

Observations

The photomicrographs and drawing in Figures 1 to 18 have been prepared to show some major trends in development which may lead to a large proliferative tumor. The specific data for each figure are given in Table I. Cases have been selected to illustrate a wide range (0.1 to 88.4 per cent) of lymphoid involvement. They have been chosen also to show focal, perivascular, and diffuse lesions. In some cases both the smallest and largest lymphoid areas of the same section are shown so that the reader may judge for himself whether there exist any fundamental histologic differences between the two. Lymphoid areas from most resistant to most susceptible lines are included to bring out any differences which may be related to these variables. One drawing was made to show the details revealed by the microscope in the hope

that it might aid in the interpretation of the less distinctly seen structures shown in the photomicrographs.

A study of the 319 slides involved in this experiment showed only one case which histologically was strikingly different from all of the others. It is shown in Figures 17 and 18 and came from a section having 88.4

TABLE I

Data Relative to Figures 1 to 18

Figure no.	Chicken no. (1945 population)	Gross diagnosis for lympho-matosis	Line of chickens	Per cent* of lympho-matosis in line	Per cent of lymphoid area for the section	Number of lymphoid areas in the section	Area in sq. mm. of lymphoid accumulation from which photomicrograph was taken
1	620K	—	13	44	0.1	1	0.02346
2	1280	—	3	67	0.4	5	0.00323
3	263X	—	6	9	0.4	5	0.00427
4	263X	—	6	9	0.4	5	0.05334
5	574B	V	12	100	0.8	6	0.07933
6	267T	—	6	9	1.6	8	0.10135
7	354H	—	9X10	40	1.8	25	0.00085
8	354H	—	9X10	40	1.8	25	0.08658
9	354H	—	9X10	40	1.8	25	0.00654
10	354H	—	9X10	40	1.8	25	0.00654
11	357Q	—	9X10	40	3.2	29	0.00128
12	357Q	—	9X10	40	3.2	29	0.07208
13	132A2	—	3	67	8.8	34	0.01067
14	132A2	—	3	67	8.8	34	0.18847
15	739E	NV	15	64	29.3	19	0.01422
16	739E	NV	15	64	29.3	19	2.07848
17	321B2	O	7	33	88.4	9	16.25600
18	321B2	O	7	33	88.4	9	16.25600

N = Neural lymphomatosis.
V = Visceral lymphomatosis.
O = Ocular lymphomatosis.
— = Negative for lymphomatosis.
* Population corrected for deaths not associated with gross tumors.

per cent of lymphoid involvement. This case was neoplastic but in the same slide certain areas were found having the histologic character of the reactions shown in the preceding figures. The remaining cases were examined to determine if there was a series of precursory reactions taking place.

Nuclear Size

One generally accepted criterion of a lymphoid tumor is the presence of lymphoid cells with large nuclei and a clumping of chromatin around enlarged nucleoli. In Figures 1 and 2 (0.1 and 0.4 per cent involvement) there are a few medium-sized nuclei. They are more conspicuous in the large diffuse area (Fig. 1) than in the small perivascular area (Fig. 2). The first figure is from a more resistant line than the second one. Figures 3 and 4 are the smallest and largest foci from a case selected from the most resistant line of the Laboratory stock. The histologic character of the two is considerably different; the small area seems relatively

unreactive, whereas in the larger area there exist fibroblasts, macrophages, one mitotic figure, and destruction of adjacent tissue. Yet the medium-sized proliferative cells such as are seen in Figure 1 are absent. In Figure 5, which is taken from a case showing a relatively small amount of lymphoid tissue (0.8 per cent), there are numerous medium-sized nuclei, but it should be pointed out that this line had more lymphomatosis than any other. This bird was the only survivor of the line, and when killed showed gross visceral involvement of liver, spleen, and kidney, although the pancreas was considered negative. Only one or two nuclei of medium size can be seen in Figure 6 (1.6 per cent lymphoid tissue). This case had the largest amount of lymphoid tissue of any survivor from the most resistant line of the Laboratory flock. The area from which Figure 6 was taken was larger than that used for Figure 5.

Figures 7 to 10 are from one case of the 9 × 10 cross in which the section showed 1.8 per cent involvement. The area shown in Figure 7 is the smallest and has 1 mitotic figure and perhaps 2 or 3 slightly larger nuclei but they are not equal to those shown in Figure 5. Figure 8 is from the largest lymphoid area of the section and shows several medium-sized lymphoid nuclei and abundant examples of gradation in nuclear size down to those of small lymphocytes. The lymphoid area shown in Figures 9 and 10 would be considered relatively small on the distribution curve for size of individual lymphoid areas; only 5 of the 25 foci in this section were smaller, yet it shows the same general characteristics as did the largest area of the section. In these figures there are several lymphocytes with nuclei of medium size, a few macrophages, some fibroblasts, and 5 mitotic figures. Figures 11 and 12, also from the 9 × 10 cross, are the extremes in size from a case which had 3.2 per cent lymphoid tissue in the section. Medium-sized lymphoid nuclei are conspicuous in both figures.

Figures 13 and 14 illustrate the extremes in size from a case showing 8.8 per cent lymphoid tissue and 34 separate foci. The lymphoid area in the latter figure was almost 0.2 sq. mm., yet in this bird there seemed to be no greater number of medium-sized lymphoid nuclei than in Figure 2, which was taken from line 3 also but had only 0.4 per cent lymphoid tissue. The case with 8.8 per cent lymphoid tissue, however, showed clear evidence of acinar destruction (Figure 14).

Figures 15 and 16 again illustrate the extremes in size of lymphoid areas and these are from a case in which 29.3 per cent of the section was involved. The largest area was over 2 sq. mm. The case was diagnosed grossly as both neural and visceral but the pancreas was negative. Line 15 from which it comes is relatively susceptible to lymphomatosis,

yet in spite of these various favorable circumstances there were very few medium-sized lymphoid nuclei. There is, however, more nuclear degeneration (Fig. 16) than in the preceding examples and there is some tissue disorganization. However, cytologic and histologic changes in the lymphoid tissue itself are not sufficiently distinctive from other cases which have much smaller amounts of lymphoid tissue to warrant use in differentiating between a positive and negative microscopic diagnosis.

The case represented by Figures 17 and 18 has been mentioned and shows a condition which probably could be correctly classified as neoplastic. Since all photomicrographs are of the same magnification, the increase in size of the lymphoid nuclei is evident. Mitotic figures are seen in both fields and abnormal mitotic figures were found.

As to size the lymphoid nuclei have shown a predominance of small and medium types, and only in the case with maximum proliferation were large lymphoid nuclei found. Much has been written about the large lymphocyte or hemocytoblast. Is it what has been called here a medium-sized lymphoid cell or is it the very large cell type shown in Figure 18? If the presence of the latter is the criterion for microscopic diagnosis, then only 1 of 319 cases would be classified as microscopically positive and those having 2 to 30 per cent of lymphoid tissue would have to be classed as microscopically negative.

Type of Lesion

Investigators working with lymphomatosis have observed various types of lymphoid lesions: (1) focal with a bounding connective tissue capsule, (2) focal without a capsule (perivascular), and (3) diffuse types. There seem to be no fundamental differences among various types and probably they represent merely the varied reaction which the lymphoid cells are capable of showing under different environmental conditions in the tissues, such as have been suggested as factors in hematopoiesis. Connective tissue acts as a natural barrier and is probably effective in restraining the migration of lymphoid cells. Numerous foci showed encapsulation by connective tissue, and examination of those which were small seemed to show a graded series of changes leading to intravascular stasis which might possibly have its origin in the sludging phenomenon of blood described by Knisely, Bloch, Eliot, and Warner.[16] Intravascular lymphoid reactions are common in chicken tissues but their relationship to lymphomatosis has not been satisfactorily determined. An example of such a reaction is shown in Figure 1 and may represent the initial stages in a focal tumor. The structure shown in

Figure 7 probably was an artery, but circulation stopped, or at least slowed down, so that mitosis took place. The central area in Figures 9 and 10 is surrounded by connective tissue remnants of the vascular wall which probably has been expanded by mitotic activity. Growth of lymphoid nodules by mitosis in birds has been mentioned by Jordan.[6] The process, once started, can continue and great expansion ultimately results (Fig. 12) so that the encapsulated area is much larger than the vessel from which it probably arose. The intravascular plug and its expansion usually are characterized by a closer aggregation of the cells than occurs in perivascular areas. Eventually the connective tissue remnants break down and the adjacent areas merge. Numerous examples of this were observed. Histologic evidence of the continuity of a focal area, such as shown in Figure 9, with the lumen of a patent vessel has not yet been observed and thus it is assumed that during development the involved vessel degenerates and becomes detached. The evidence indicates that stasis and lymphocytic development start in small vessels rather than in larger ones, but apparently not in capillaries. This may help to explain the observations made in an earlier report[17] that lymphoid accumulations rarely, if ever, originate in the pancreatic islets, which contain primarily a capillary circulation.

Foci which originate as perivascular areas are more loosely bound by a network of connective tissue (Figs. 2 and 3) than are the intravascular, focal areas. As they proliferate they are only partially restrained by the connective tissue (Fig. 13) and displacement of adjacent normal parenchymal tissues often has been observed.

In the diffuse type the lymphoid cells which chance to accumulate in the sparse connective tissue around the acini are apparently the least restricted in their migration (Fig. 1). This type is relatively rare in the pancreas. When it occurs it is destructive to the adjacent acinar and islet tissues. It has been observed in some cases that the encroaching focal or diffuse lymphoid tissue was destroying intrinsic ganglia of the pancreas, but never has a small focal area appeared to have its origin within a ganglion. This was surprising in view of the fact that the larger visceral ganglia are reported to have lymphoid areas.[7] The same explanation given for the islets is probably applicable here, that the vessels of these small intrinsic ganglia, which seldom show more than 3 or 4 cells in one cross section, are limited to capillaries.

For diagnostic purposes in determining whether a bird has lymphomatosis, there seems to be little practical value in separations based on the type of lymphoid involvement, especially since very frequently all types can be found in the same section.

Discussion and Conclusions

Can any lymphoid accumulation in a parenchymal organ such as the pancreas be regarded as normal for the bird? It has been suggested by others[1-4] that such lymphoid accumulations exist because most birds do not have lymph nodes as do mammals, yet it has been pointed out in this study that some lymphoid areas arose from occluded vessels, which obstruction can hardly be regarded as normal for the vascular system; others are perivascular and sometimes cause the vessel wall to bulge into the lumen, which again can hardly be considered normal and possibly interferes with the flow of blood. Invasive lymphoid areas show histologic evidence of destruction of acinar tissue, pancreatic islets, and intrinsic nerve ganglia, as well as displacement of these tissues. Thus, histologically, there seems little evidence that any ectopic lymphoid accumulation is normal for a healthy chicken. True, its presence may possibly indicate a desirable defense reaction, but it has already been pointed out that there is a difference in the way one should regard aggregations of lymphoid tissue in organs such as the thymus, bursa, and spleen, which develop in anticipation of future needs, and lymphoid foci which arise in response to a foreign stimulus. The former has been called normal and the latter abnormal, or at least indicative of pathogenic agents at work.

It is obvious, of course, that it would be simpler to classify only those tumors showing very large lymphoid cells and wild proliferation, such as pictured in Figures 17 and 18, as microscopically positive for lymphomatosis and all other cases as microscopically negative. To do so, however, immediately raises several difficulties in that small lesions in the nervous system conventionally diagnosed as positive for lymphomatosis often do not show large lymphoid cells or a reaction suggestive of neoplasia, but the general evidence of association with other features of this disease seems to justify including the neural form in the disease complex. Likewise, one is faced with the problem of evaluating a section in which up to 29 per cent of the area is lymphoid and yet is otherwise little different histologically from sections in which the amount is small.

It becomes extremely difficult and probably impossible on the basis of histologic evidence alone to set forth clear-cut lines of separation between hyperplastic and neoplastic reactions. In the sections studied there are all gradations from small perivascular areas, which seem to be doing no harm, up to large destructive lymphoid proliferations. There is no more basis for regarding a minimal amount of lymphoid tissue as normal than there is for considering it abnormal. The chief arguments for its normality are its widespread distribution among birds and, by

comparison, its uncommon occurrence in mammals which have lymph nodes, but these points do not constitute factual evidence for normality in the sense in which the term "normal" has been used in this paper. Kelsall[18] has made the interesting observation that the presence of large mixed cell sarcomas in rats did not change the size or shape of lymphocytes from those present in the intestine of control animals. Kelsall and Crabb[19] later showed that the liver of hamsters, which does not normally have lymphoid areas, will develop periportal lymphocytes and plasma cell infiltrations with hematopoiesis, shortly following subpannicular implantation of a mixed cell sarcoma.

Over 20 years ago Pappenheimer, Dunn, and Cone[7] were impressed by the fact that there was very little difference in the lymphoid picture of birds showing grossly visible lesions and the ones which did not. They suggested that many birds believed negative for lymphomatosis very probably were under stimulation of the agent and in their opinion microscopic diagnosis was arbitrary. However, our report presents some evidence for the abnormality of the occurrence of ectopic lymphoid areas and emphasizes that qualitatively, at least, no histologic evidence exists which precludes the possibility that even minimal amounts of lymphoid tissue are indicative of the agent responsible for lymphomatosis.

Summary

A histologic study was made of lymphoid areas found in one section from each of 319 survivors of an original population of 1123 chickens. These represented 14 inbred lines and a cross between two of the lines.

The pancreas was grossly negative for lymphoid tumors in every case.

The amount of lymphoid tissue in the pancreas varied from none to 88.4 per cent of the section and from none to 34 separate foci. Only in the case with 88.4 per cent of lymphoid tissue was the histologic picture sufficiently distinctive to separate it clearly from the other cases. Throughout the range from amounts of less than 0.1 per cent to 30 per cent there were no distinctive histologic criteria which, independent of quantity, could form a basis for diagnosis. Nor did resistance, susceptibility, hybridization, or inbreeding appear to be regulating factors in the histologic picture.

Focal areas bounded by connective tissue were interpreted as derived from plugged and expanded blood vessels. It was suggested that the diffuse and invasive character of the lesions was influenced, at least in part, by the connective tissue matrix of the lesion and that, on that basis, the type of lesion had no great value in arriving at a diagnosis

of lymphomatosis, although some types of lymphoid lesions may be more damaging than others.

Consideration was given to the problem of the normality of any lymphoid foci in the pancreas and, in view of the numerous examples of destructive action of these lymphoid areas, the normality of all of them is questioned. Moreover, a review of evidence in the literature reveals no convincing basis for their normality.

Acknowledgment is made to Janet B. Breitmayer for technical assistance in this study.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATES 184–188

Figures 1 to 18 are presented to show the histopathologic variations in representative lymphoid areas. The photomicrographs were taken at an optical magnification of 762 times and the drawing was made at an optical magnification of 645 times. Magnification for publication is 639 × for all figures except Figure 10 which is 941 ×. The magnification of Figure 9 after reduction is 516 ×.

The salient data concerning each figure have been presented in Table I in the text.

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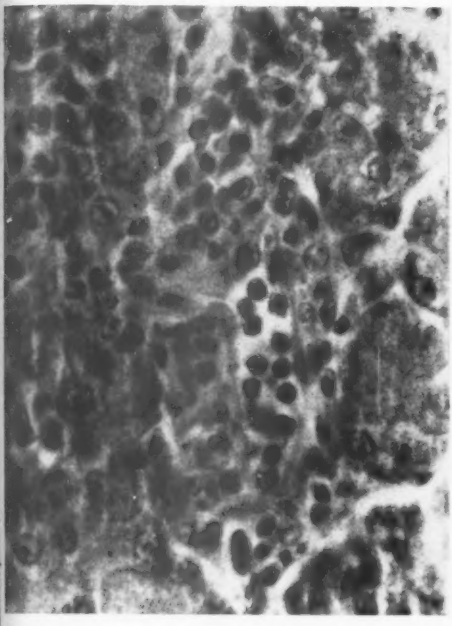

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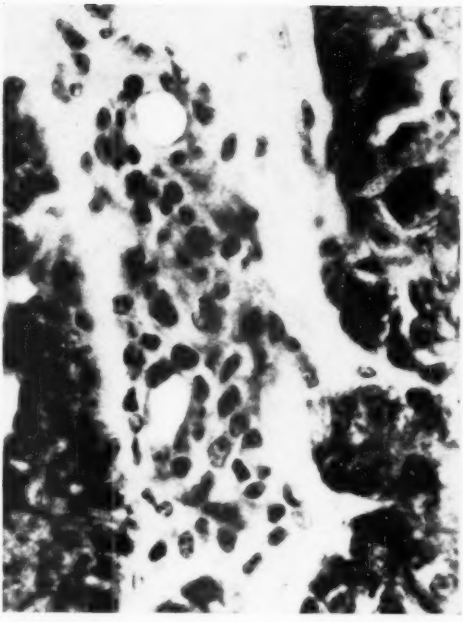

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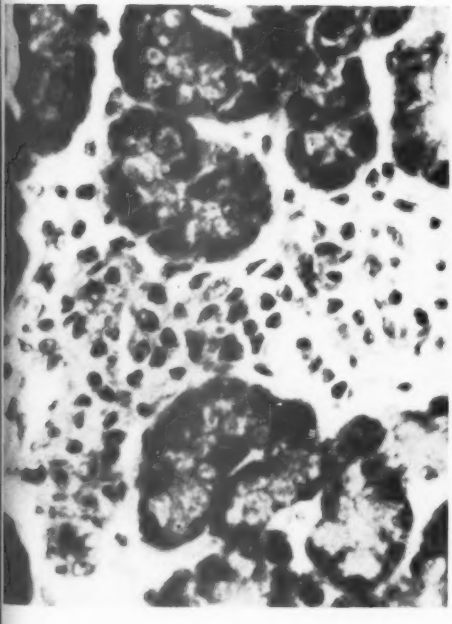

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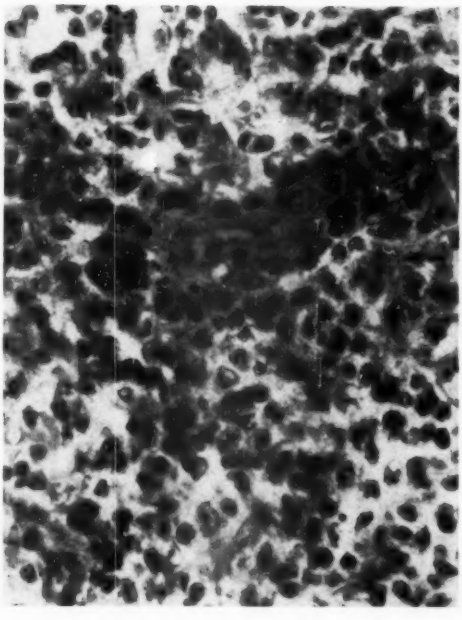

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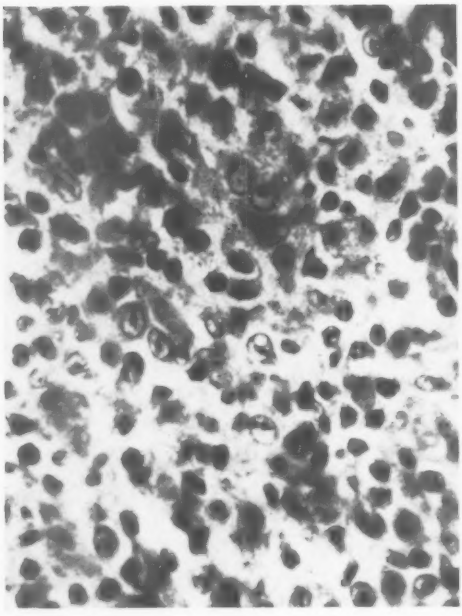
Lymphoid Areas in the Pancreas



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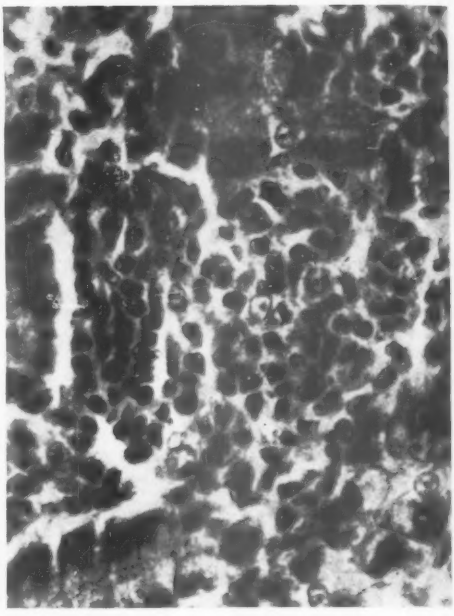

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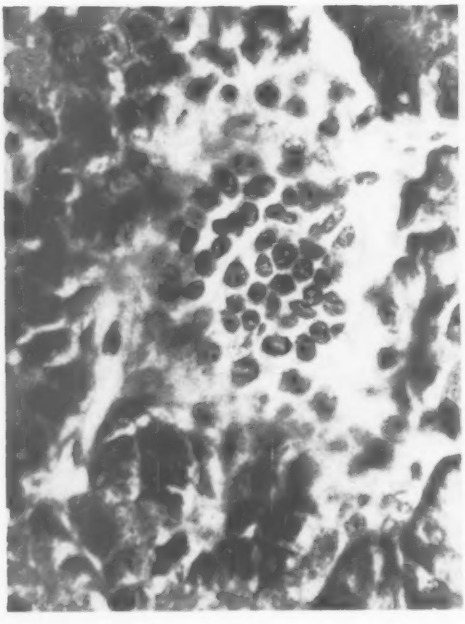

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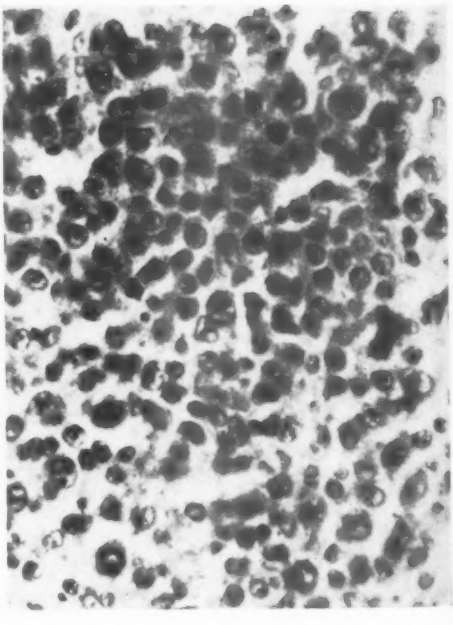

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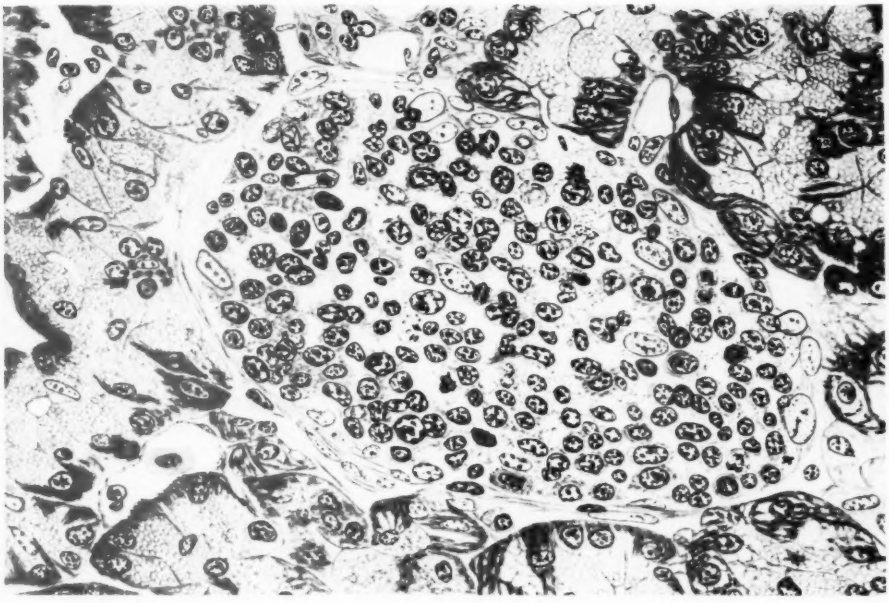
Lucas Lymphoid Areas in the Pancreas



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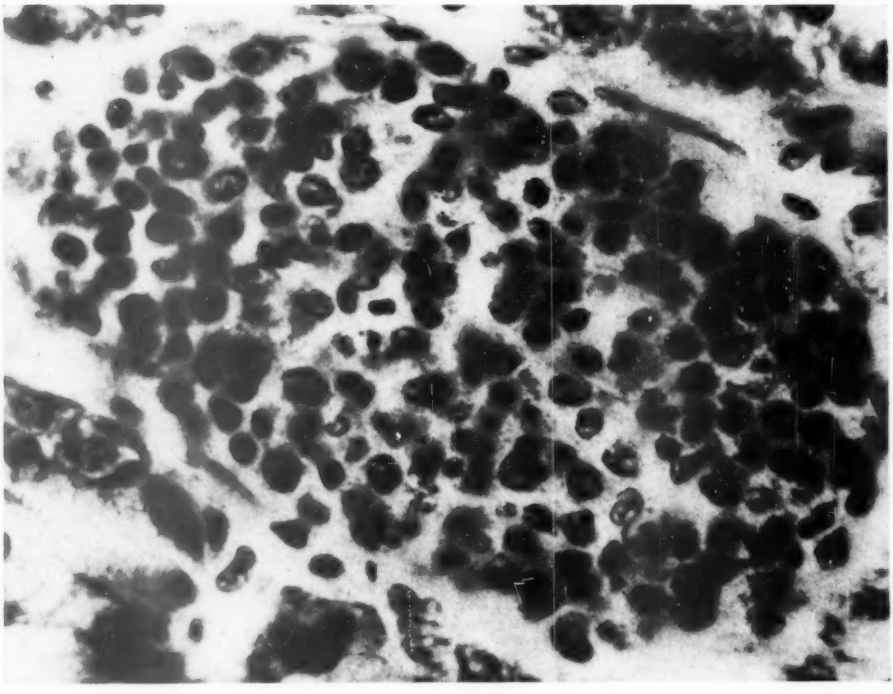

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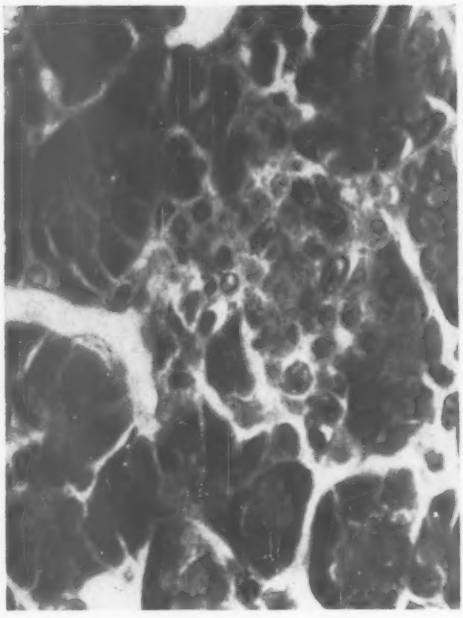

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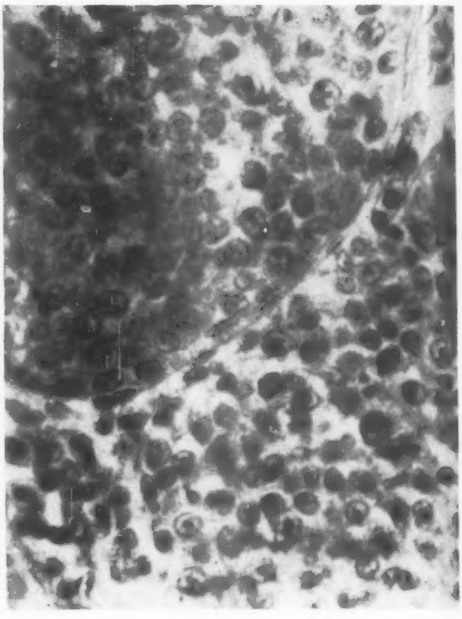

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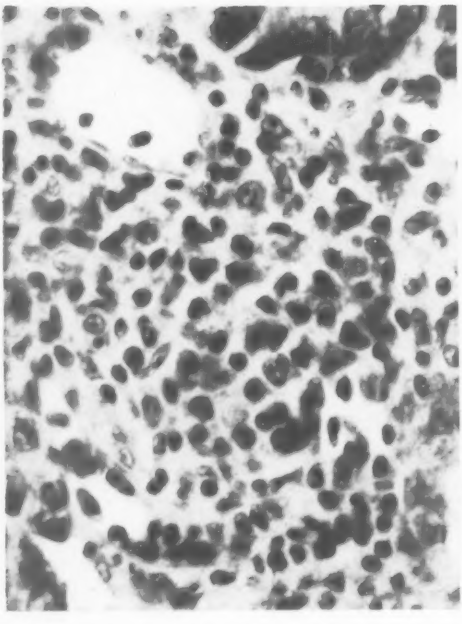

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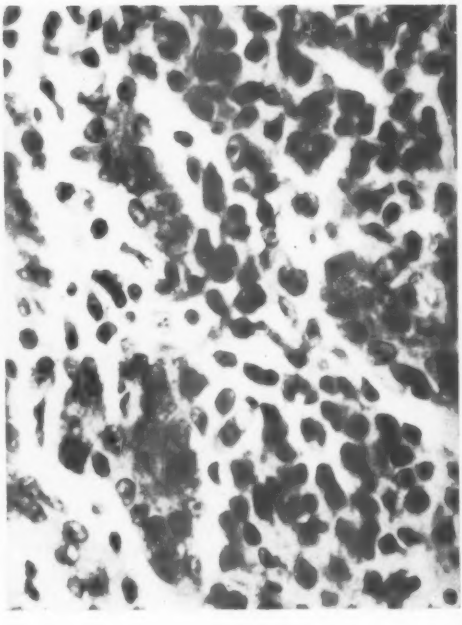

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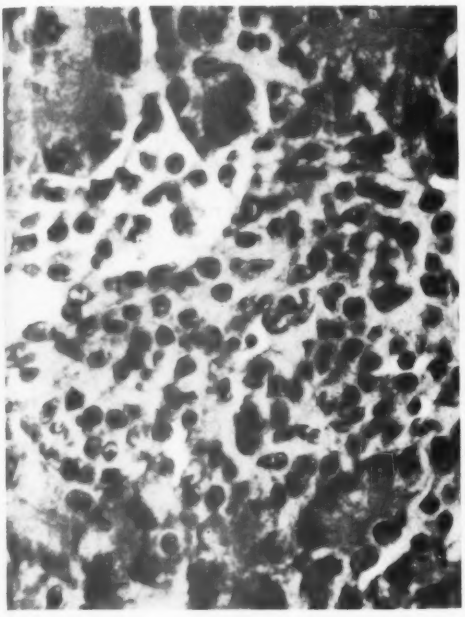
Lucas Lymphoid Areas in the Pancreas



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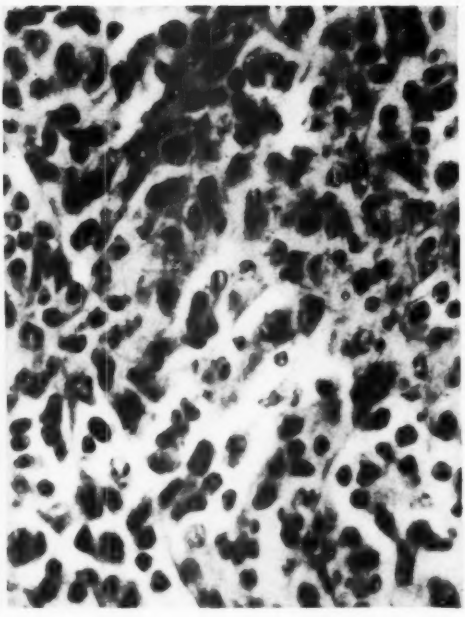

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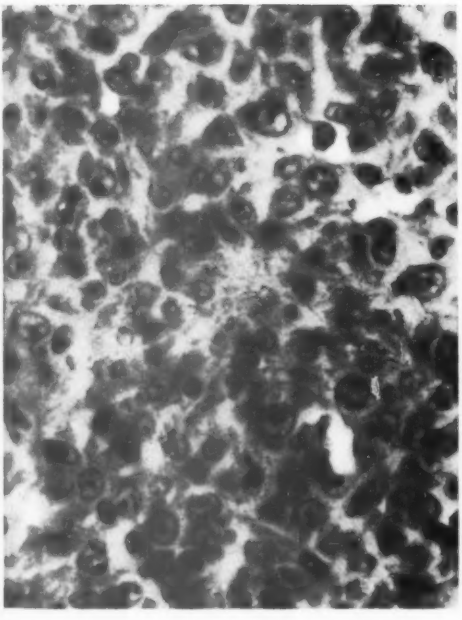

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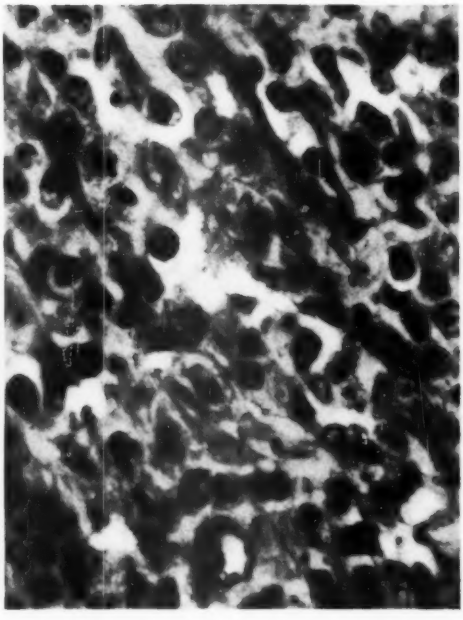

18

SPONTANEOUS CARDIAC LESIONS IN MICE
THEIR BEARING ON ATTEMPTS TO PRODUCE EXPERIMENTAL CARDITIS*

FRIEDA G. GRAY, M.D.†

(From the Section of Preventive Medicine, Yale University School of Medicine, New Haven, Conn.)

Following the method of multiple parenteral injection of foreign protein used by Rich and Gregory[1-3] and others[4-6] to produce lesions of rheumatic and periarteritic type associated with anaphylactic hypersensitivity, Moore and his co-workers,[7] in 1947, reported the occurrence of "rheumatic-like" cardiac lesions in mice given multiple parenteral injections of diluted egg white. They stated that all their mice, whether sensitized by the intravenous or intraperitoneal route, developed lesions resembling those seen in acute rheumatic carditis in man and those described by Rich and Gregory[2,3] in rabbits. They pointed out that some untreated mice had minimal lesions which they called "rheumatic stigmata" but that these lesions were neither as frequent nor as marked as those in treated animals.

The present report deals with an attempt to repeat the work of Moore and his associates.[7] It was found that normal mice showed spontaneous cardiac lesions similar to those reported in their treated mice. The incidence and severity of the spontaneous cardiac lesions reported here were not increased by multiple parenteral injections of diluted egg white.

MATERIALS AND METHODS

Egg white, separated from the yolks of 1-day-old hens' eggs, was beaten to break up the mucin sacs, filtered through several layers of gauze, diluted with nine parts of sterile distilled water and then refiltered to remove the precipitated mucin. Each of the mice inoculated intraperitoneally received 1 cc., and each of the mice inoculated intravenously received 0.2 cc. of diluted egg white prepared immediately before injection. All mice treated with multiple injections received them at weekly intervals.

The "typhoid free" white Swiss mice, 3 weeks of age, used in the experiments, were all obtained on the same day from one dealer so that treated mice and controls were comparable as to source, age, diet, and housing conditions. Mice killed or dying as a result of inoculation were immediately autopsied and the organs fixed in formalin. The hearts were semi-serially sectioned at levels which would permit observation

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of all valves. From 10 to 40 sections of each heart, stained with hematoxylin and eosin, were examined microscopically.

Experimental Findings

In the attempt to produce cardiac lesions in mice made hypersensitive to diluted (1:10) egg white, 145 mice were used. One hundred were given multiple parenteral injections and 45 mice were used as controls.

Initially, each of the 100 treated mice received three weekly intraperitoneal injections of freshly prepared egg white and the 96 survivors were divided and variously treated so that at the conclusion of the experiments the hearts of five groups of mice treated in different ways (Table I) were sectioned: Group A, those surviving four intraperitoneal

Table I

Number of Mice and Variation in Treatment

	Number treated	Route and number of injections	Number examined microscopically
Group A	23	4 I.P.*	21
Group B	26	3 to 11 I.P.	19
Group C	15	3 I.P. and 1 I.V.†	13
Group D	32	3 I.P. and 1 to 5 I.V.	30
Group E	4	11 I.P. and 1 to 3 I.V.	3
Total treated	100		86
Group F	25	1 I.V.	19
Group G	20	None	20
Total controls	45		39

* I.P. = intraperitoneal.
† I.V. = intravenous.

injections and killed at weekly intervals without further injections; group B, those dying of anaphylactic shock as a result of the third or subsequent weekly intraperitoneal injections (up to nine doses); group C, those surviving three intraperitoneal and one intravenous injections and thereafter killed at weekly intervals; group D, those surviving three intraperitoneal and one intravenous injections but dying of anaphylactic shock as a result of subsequent intravenous injections; group E, 4 mice surviving eleven intraperitoneal injections and dying of anaphylactic shock after subsequent intravenous injections.

Anaphylactic hypersensitivity to diluted egg white was produced frequently as evidenced by death due to anaphylactic shock occurring within ½ hour after inoculation. There was a progressive increment of anaphylactic deaths with each successive injection after the third, the increment being greater with the intravenous than with the intraperitoneal route.

Two groups of control mice were used in the experiments. The first, group F (25 mice), received a single intravenous injection of diluted egg white on the same day that mice treated with multiple injections received their fourth dose. The second, group G (20 mice), were untreated. The mice in each group were killed and autopsied at weekly intervals so that the ages in the control groups were comparable to those in all of the treated groups.

Eleven mice found dead from 2 to 18 hours after an injection and 9 mice (3 treated and 6 controls) found dead at times unrelated to injections were excluded from microscopic study because they were partly eaten or their organs autolyzed.

At autopsy, no gross abnormalities of the unopened heart were seen in any of the mice. Microscopic examination revealed cardiac lesions in a large percentage of both treated and control mice (Table II) without

TABLE II

Incidence of Combinations of Different Types of Cardiac Lesions in Control and Treated Mice

	Total no. of mice	Total with lesions		One type		Two types		Three types		Four types		Five types	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Treated	86	71	82.6	22	25.6	22	25.6	17	19.8	7	8.1	3	3.5
Control	39	28	71.8	12	30.8	10	25.6	2	5.1	3	7.7	1	2.6

All percentages given are of the total number of mice examined in each group.

statistically significant difference in frequency and severity between the two groups. These lesions consisted of accumulations of cells of varying size in the myocardium, valve leaflets, endocardium, pericardium, and about the coronary vessels. The cellular elements in all of these sites were similar, consisting predominantly of lymphocytes, plasma cells, large mononuclear cells, "Anitschkow myocytes," and rarely neutrophilic polymorphonuclear leukocytes and large cells with one or more nuclei and basophilic cytoplasm.

In the valve leaflets these accumulations varied from a few cells beneath the endocardium of the superior surface of the leaflet to large focal accumulations which enlarged and distorted the leaflet (Figs. 1, 2, 3). At times diffuse infiltration of the entire leaflet and its chordae tendineae was present. The mitral was the valve most frequently involved and occasionally there were multiple foci in the same leaflet or in two leaflets. In only rare instances were accumulations seen in the aortic or tricuspid leaflets.

Small collections of the described cells in the myocardium (Fig. 4), with some tendency toward perivascular localization and a distinct predilection for the base of the interventricular septum, comprised the

most frequent lesion observed in both the control and treated mouse hearts. Fatty and hydropic degeneration and fragmentation of muscle fibers were frequently present with the cellular infiltration. Focal accumulations of the same cellular elements were seen in the pericardium and endocardium (Fig. 5) and, when present, most commonly involved the right atrium. Perivascular infiltration of a minor degree was common about the small and medium-sized coronary arteries (Fig. 6) and consisted of cells similar to those in the other lesions. In some instances the infiltrations were more dense, and in these an occasional cell resembling an Aschoff cell was present. In no instance, however, was a true "Aschoff nodule" observed nor was there collagen degeneration of the coronary vessels or perivascular tissues. An acute segmental fibrinoid degeneration of the aorta and main pulmonary artery with infiltration of polymorphonuclear leukocytes in the wall and surrounding tissue, resembling human periarteritis nodosa, was encountered in a very few instances (Fig. 7).

"Valvulitis" and perivascular infiltrations are considered here as the more significant from the standpoint of "rheumatic-like" lesions. The incidence of these lesions and of the other types described is given in Table III. In no instance is the difference in incidence between the treated and control groups of significance when the results are subjected to statistical analysis (X^2 test).

TABLE III

Incidence of the Different Types of Lesions in Treated and Control Mice

	Total no. of mice	Valvulitis		Perivascular infiltration		Myocarditis		Endocarditis		Pericarditis	
		No.	%	No.	%	No.	%	No.	%	No.	%
Treated	86	33	38.4	36	41.9	59	68.6	13	15.1	15	17.4
Control	39	8	20.5	11	28.2	25	64.1	9	23.1	3	7.7

All percentages given are of the total number of mice examined in each group.

The total incidence of one or more lesions in each group and the frequency of occurrence of combinations of the different lesions are given in Table II. There is no statistically significant difference between the treated and control groups in the total number of mice showing one or more lesions or showing different combinations of these lesions. Each of the lesions occurred alone but none with any more frequency than the others. All possible combinations of the lesions occurred, and here again no one combination was present with more regularity than any other. It is apparent from the table that slightly more than half of the mice had one or two of the different types of lesions while in only a very few were all of them present.

The severity of the lesions was arbitrarily graded from 1 plus to 3 plus and the incidence of the three grades compared in the treated and control groups (Table IV). Here again, no statistically significant difference between the two groups was found.

TABLE IV

Severity of the Different Types of Lesions in Treated and Control Mice

	Total no. of mice	Valvulitis			Perivascular infiltration			Myocarditis			Endocarditis			Pericarditis		
		+	++	+++	+	++	+++	+	++	+++	+	++	+++	+	++	+++
Treated	86	13.9	13.9	10.5	33.7	8.1	0	39.5	22.1	6.9	15.1	0	0	13.9	1.2	2.3
Control	39	0	12.8	7.7	15.4	10.3	2.6	33.3	23.1	7.7	15.3	5.1	2.3	5.2	0	2.6

Figures given are percentages of the total number of mice examined in each group.

It may be stated that among the treated mice there was no statistically significant difference in the incidence or severity of lesions between those treated by intravenous and intraperitoneal injections of egg white; there was no difference between the mice which received only four injections and those which received five to fourteen; moreover, there was no difference between those dying of anaphylactic shock and those which survived multiple injections and were killed at intervals of 1 week. In the control group, there was no difference in the incidence or severity of lesions between those which were given a single injection of egg white and those not given any injections. Analysis of all the mice on the basis of age revealed no difference among those which died or were killed at intervals of 5½ to 16½ weeks.

DISCUSSION

The results indicate that the normal Swiss mice of a "typhoid free" strain used in these experiments frequently have spontaneous cardiac lesions which are prominent. Treatment of these mice with multiple parenteral injections of diluted egg white produced anaphylactic hypersensitivity but failed to increase the incidence or severity of these lesions and also failed to produce cardiac lesions of any other type. In spite of the infrequent presence of collagen degeneration, such other features as the distribution of the spontaneous lesions, their cellular elements, and the occasional occurrence of segmental arterial fibrinoid degeneration indicate that these lesions are similar to those experimentally produced in rabbits in association with anaphylactic hypersensitivity.

Moore and his co-workers,[7] using a "typhoid resistant" strain of mice raised in their laboratory, reported that all their mice given multiple parenteral injections of diluted egg white developed cardiac lesions of the rheumatic type. However, they noted lesions of the same type in their

control mice but these were less frequent and less severe than in the treated group. The combination of a greater dosage of foreign protein and a different strain of mice used by these workers may be responsible for the greater incidence and severity of the lesions reported by them in treated mice.

Lesions similar to those described here but more characteristic of Aschoff nodules have been described in mice by Lenke and Loewe,[8] who believed them to be due to a spontaneous disease in mice resembling the rheumatic process in humans. Moore and his associates[7] believed that the cardiac lesions seen in their mice were the result of hypersensitivity to some factor in the mouse environment. We offer no suggestion as to the nature of the lesion in our own stock mice. Nevertheless, because of the frequency and severity of the cardiac lesions in normal animals, whether due to a latent infection, hypersensitivity to some environmental factor, or other unknown causes, these mice are obviously unsuitable for experiments in which the occurrence of "rheumatic-like" lesions is a determining factor in the interpretation of the results.

Summary and Conclusions

A high percentage of Swiss mice used as controls were found to have cardiac lesions resembling those of the rheumatic type associated with experimental anaphylactic hypersensitivity.

Treatment of these mice with multiple parenteral injections of egg white, although it produced anaphylactic shock, failed to influence the incidence and severity of these lesions and did not produce other cardiac lesions.

The high incidence and the severity of the cardiac lesions in the control mice used in these experiments indicate that some mice are unsuitable for the experimental investigation of hypersensitivity as related to the production of "rheumatic-like" lesions.

The cause of the observed cardiac lesions was not determined.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 189

FIG. 1. Heart of control mouse, showing an accumulation of cells beneath the endothelium of the mitral valve with enlargement and distortion of the leaflet. Hematoxylin and eosin stain. × 150.

FIG. 2. Higher magnification of the leaflet seen in Figure 1, to show cellular elements. Hematoxylin and eosin stain. × 600.

FIG. 3. Mitral valve of another control heart to show focal accumulation of cells. Hematoxylin and eosin stain. × 600.

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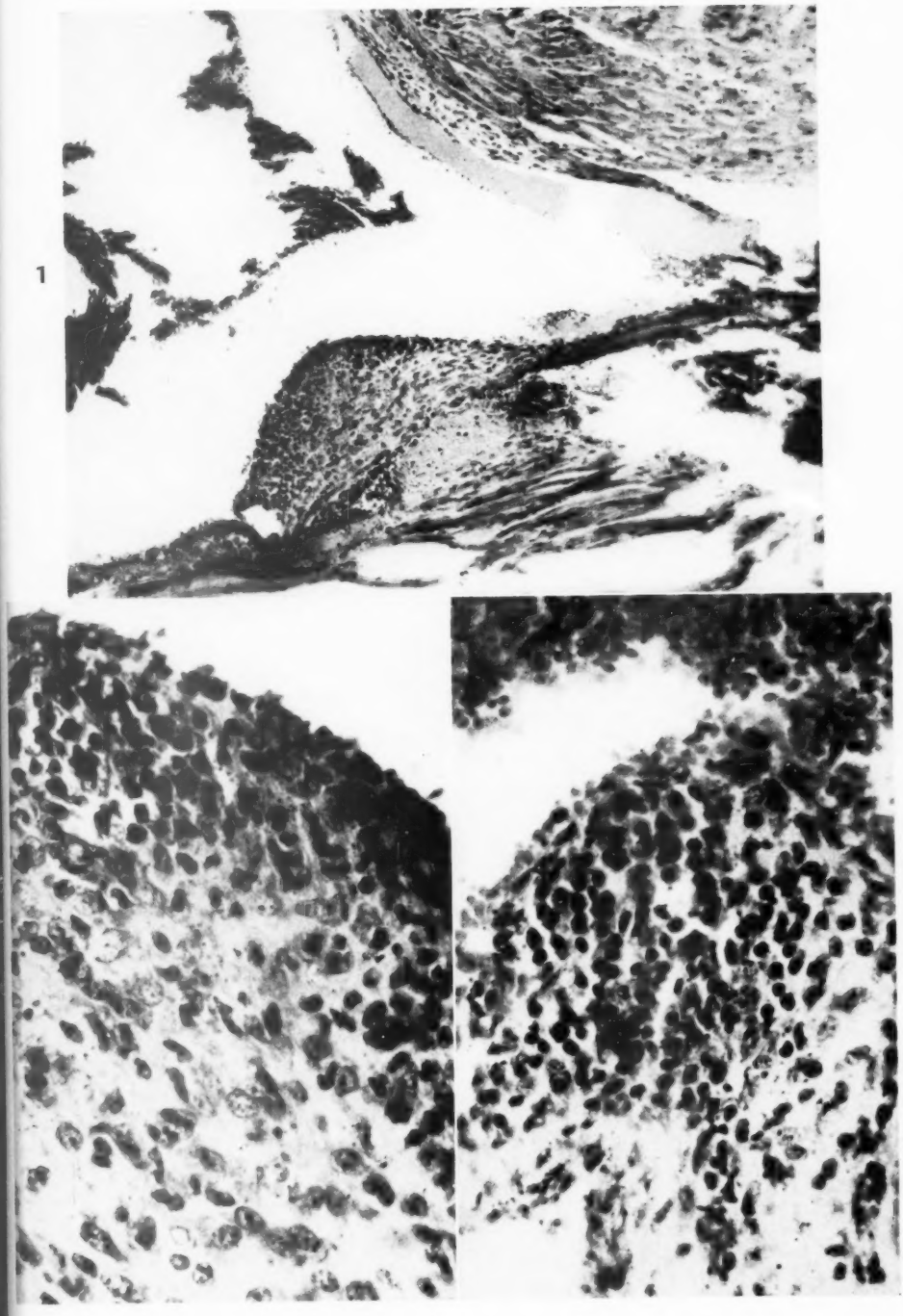

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Spontaneous Cardiac Lesions in Mice

PLATE 190

FIG. 4. Focal interstitial collection of cells in myocardium of heart of control mouse. Hematoxylin and eosin stain. × 300.

FIG. 5. Left atrium of a control heart showing cellular infiltration of pericardium and endocardium. Hematoxylin and eosin stain. × 245.

FIG. 6. Slight infiltration about a coronary artery in a control heart. Hematoxylin and eosin stain. × 510.

FIG. 7. Ascending aorta of a control mouse showing segmental degeneration and cellular infiltration. Hematoxylin and eosin stain. × 360.

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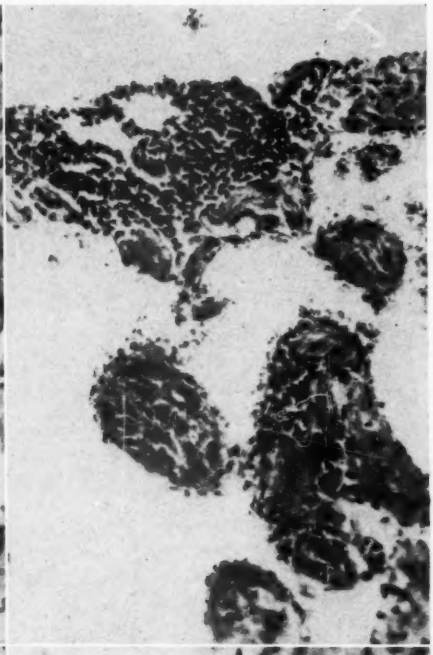

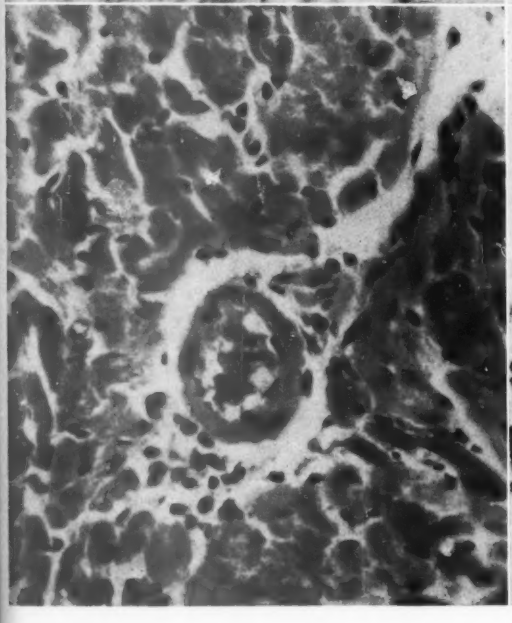

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Gray Spontaneous Cardiac Lesions in Mice

CHRONIC PANCREATITIS AND LITHIASIS

I. A Clinicopathologic Study of 62 Cases of Chronic Pancreatitis*

Hugh A. Edmondson, M.D., Weldon K. Bullock, M.D., and John W. Mehl, Ph.D.

(From the Departments of Pathology and Biochemistry, School of Medicine of the University of Southern California, and the Laboratory of the Los Angeles County Hospital, Los Angeles, Calif.)

The relationship of chronic pancreatitis to antecedent acute attacks of the disease and to complications such as lithiasis, diabetes mellitus, and steatorrhea is gradually undergoing clarification. Pathogenesis and treatment are still major problems. The more complete elucidations of the clinical course and natural history of the primary disease of the pancreas uncomplicated by any disease of contiguous organs has recently been given by Comfort, Gambill, and Baggenstoss,[1] and by Maimon, Kirsner, and Palmer.[2] These workers have used the terms "chronic relapsing" and "chronic recurrent" pancreatitis to indicate the repetitive nature of the injury to the organ, presumably by acute episodes of one form or another.

In approaching the problem from the standpoint of pathology and attempting to correlate such clinical and physiologic data as seem applicable, we have reviewed the records of 33,500 consecutive autopsies at the Los Angeles County Hospital from August 31, 1926, to March 1, 1947. All instances of moderate to severe chronic diffuse pancreatitis and/or calculi have been used for this study. Excluded are those in which pancreatitis was secondary to perforating peptic ulcer or to obstruction of the ducts by carcinoma. Those with interacinar fibrosis alone, atrophy, and diabetes were not used. Particular attention has been paid to the genesis of calculi, and for that reason part II of this series† will be devoted entirely to that subject.

Historical Literature

A complete review of the literature of chronic pancreatitis will not be attempted. Chronic pancreatitis was a more popular subject for authors before the time of Opie's contribution than it has been in recent decades. Opie[3] devoted a chapter numbering 39 pages to its discussion in 1910. Authors of recent textbooks of pathology have given a surprisingly small amount of space to it, or have failed to mention it altogether. The development of the present concept of chronic pancreatitis can be traced fairly well in the works of Claessen[4] in 1842, Friedreich[5] in 1878,

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† Will appear in the January issue of this *Journal*.

Oser[6] in 1898, Opie in 1902[7] and 1910,[3] Mayo Robson and Cammidge[8] in 1907, Gruber[9] in 1929, and in the recent publications of Comfort *et al.*[1]

No one seems to have been given credit for the first valid description of the disease. Claessen,[4] in 1842, in his monograph on diseases of the pancreas stated that much confusion had existed prior to that time in regard to various states of sclerosis and hardening of the pancreas. He clearly defined chronic inflammation of the pancreas and gave criteria distinguishing it from carcinoma. He reported one case and reviewed the previously reported histories of eight others which he considered to be representative of the same disease. Claessen mentioned that acute inflammation may be present in the pancreas of patients with chronic pancreatitis at autopsy and specifically stated that acute attacks may lead to the chronic disease. He illustrated this with a case report from the literature. Probably Claessen was the first author to emphasize and define the entity of chronic pancreatitis.

Friedreich[5] differentiated between primary and secondary chronic interstitial pancreatitis. The primary form he considered extremely rare. He wrote: "The most frequent form of chronic pancreatitis is the chronic interstitial inflammation, consisting of a hyperplasia of its interacinous connective tissue and consequent atrophy, even to the entire disappearance, of the gland-substance proper."[5a] Closure of small ducts leads to the formation of cysts. Interestingly enough, he recognized the rôle of alcoholism, as did many other early authors. He stated: "I am inclined to believe that a general, chronic, interstitial pancreatitis may result from excessive alcoholism (drunkards' pancreas)."[5b] He gave a case report with autopsy to demonstrate this relationship. Also of interest in view of our present-day concept is his mention of Klob's[10] report (1860) of chalky areas and hemorrhage in the thickened connective tissue of the pancreas. This probably represents the first reported case of chronic pancreatitis with death in a recurrent acute attack. The nature of fat necrosis, of course, was not recognized until Balser's[11] publication in 1882.

Friedreich[5] listed the symptoms of steatorrhea, diabetes, chronic jaundice, epigastric pain, and weight loss much as we describe them today. No mention was made of the possibility of calculi being secondary to chronic pancreatitis, but always vice versa.

Oser[6] recognized two types of pancreatitis. The first involved the entire gland and might be due to injurious agents entering along various avenues such as vessels, ducts, and lymphatics. Biliary disease and

alcoholism were considered in the etiology. He mentioned that atrophy and fibrosis followed stasis. A second group due to penetrating lesions of the stomach and duodenum he described as circumscribed pancreatitis. Opie[7] distinguished two forms of the disease: chronic interlobular and chronic interacinar pancreatitis. Chronic interlobular pancreatitis is the more common, usually secondary to duct obstruction, and often leads to great atrophy of the organ. However, the islets are resistant to destruction and diabetes is not seen as often as in the chronic interacinar type, which produces fibrosis in the centers of the lobules. This type of disease he found more frequently associated with chronic alcoholism and cirrhosis than the interlobular form.

Quénu and Duval,[12] at the time Opie was studying the pancreas, emphasized that stones in the common duct, if there for years, would cause chronic pancreatitis.

Chronic alcoholism as a cause of chronic pancreatitis was discussed by Lefas,[13] Lando,[14] and Poggenpohl.[15] Poggenpohl further refined the descriptions of fibrotic changes in the pancreas to include periacinar and intra-acinar forms.

After Opie there is a paucity of reports of any combined clinical and pathologic studies. Most reports were of a clinical nature only, or simply case reports. Several authors postulated that chronic pancreatitis was a complication of gallbladder disease in the absence of stones in the common duct. Gruber[9] reviewed the literature and wrote a complete description of the changes in the pancreas. More recently, French workers[16,17] have described a left chronic pancreatitis characterized by pain and tenderness in the left upper quadrant with acute attacks of variable severity which tended to recur for years. The pain radiated to the left and might be confused with gastric ulcer. These authors, along with others,[18] believed that repeated attacks of edematous pancreatitis gave rise to chronic pancreatitis. That it so often affected only the left half of the pancreas they attributed to the fact that the head of the organ has a dual blood supply and drainage system. If either the duct of Wirsung or the duct of Santorini was blocked, the other would carry the external secretion to the duodenum. They pointed out that the body and tail of the pancreas, however, have only one blood supply and one duct. Thus they are more susceptible to damage by blockage of the duct of Wirsung or to any interference with the vascular supply. For this disease they performed a number of left hemipancreatectomies.

Many of the French authors,[19] as well as others, emphasized that chronic disease may involve principally the head of the pancreas, pro-

ducing icterus, and may be difficult to distinguish from carcinoma. Peterson and Cole[20] believed that there are two types of involvement of the head causing jaundice. One is a localized pancreatitis which may subside in a few months. The other is due to diffuse sclerosis of the gland and produces an irreversible obstruction or stricture of the common duct.

That repeated attacks of pancreatitis might be associated with diabetes and steatorrhea was suggested by Stern[21] in 1930 and Svartz[22] in 1931. Each reported a single case. During the acute episodes the diabetes became much worse. Although Svartz used the term "recidivating pancreatitis," the cases reported by both authors probably represent the entity now known as chronic relapsing or chronic recurrent pancreatitis. One would like to have seen higher diastase levels in both patients at the time of the acute attacks in order to make the diagnosis unequivocal.

In 1946 Comfort *et al.*[1] reported a group of 29 patients with chronic relapsing pancreatitis in whom there was no complicating disease of contiguous organs. They carefully traced the natural history of the disease, emphasizing its recurrent nature and the sequelae of steatorrhea, diabetes mellitus, and calculi. The characteristic laboratory findings of various stages of the disease were brought to light. Alcoholism was present in 68 per cent of those in whom a history of alcohol consumption was elicited. There were 3 autopsies in this group. The authors considered interstitial fibrosis and residual necrosis of tissue as the most impressive findings, probably caused by repeated attacks of edematous pancreatitis or sublethal attacks of acute hemorrhagic pancreatitis with necrosis. Pseudocysts, perineural distribution of lymphocytes, and arteriosclerosis were described also. They were the first to emphasize that calculi are often secondary to pancreatitis.

Maimon *et al.*[2] observed a group of 20 patients with the same disease and termed it "chronic recurrent pancreatitis." They discussed the symptoms, laboratory diagnosis, and treatment. One autopsy was performed but no details were given. Only 2 of the group were alcoholic.

It should be remembered that these recent investigations have delineated a clinical entity not difficult to diagnose. Whatever the clinical course, symptomless or not, the resultant pathologic changes in the pancreas constitute the same disease that has been known for over 100 years. Although the terms "recidivating," "relapsing," and "recurrent" are excellent for clinical diagnosis, the question of the wisdom of using a multiplicity of terms for the same disease arises. So, for the pathologist at least, the continued use of the simple term "chronic pancreatitis" for anatomic diagnosis seems advisable.

Clinical Features

After microscopic examination of the pancreas we discarded all cases with minimal lesions. There remained 62 instances of chronic pancreatitis among 33,500 necropsies (0.18 per cent). After a review of the clinical records an attempt was made to evaluate the problem of diagnosis and the relation of pain, alcoholism, diabetes, and jaundice to the disease. The clinical diagnoses were disappointing. Not a single case was suspected or diagnosed as having chronic pancreatitis. The explanation for this probably lies in (1) inadequate histories, (2) lack of pain as an outstanding symptom, and (3) a low "index of suspicion" on the part of the attending and resident clinical staff, who only recently have become more aware of the entity.

Epigastric pain was certainly not a prominent complaint. It was mentioned in 16 (25 per cent) but could reasonably be attributed to coronary disease, pneumonia, cholelithiasis, cirrhosis, peritonitis, or pulmonary tuberculosis. However, in retrospect it is probable that the pancreas was the source of the pain in 4 cases. A diagnosis of acute pancreatitis was established by high serum amylase values in one of the latter. However, only 2 other patients in the entire series had a diagnostic serum amylase determination.

The correlation of chronic pancreatitis with alcoholism (24 instances) and with alcoholism plus fatty cirrhosis (19 cases) was most striking. In addition, 3 patients had portal cirrhosis without a history of alcoholism. Acute pancreatitis occurring during or following the ingestion of alcohol is well known.[23-27] Paxton and Payne,[28] in a report of 307 cases from this hospital, noted a history of excessive alcoholic intake in 55 (18 per cent). Therefore it is not surprising that a considerable number of chronic alcoholic patients with cirrhosis develop chronic pancreatitis. The minor episodes leading to a scarred pancreas could have been masked by alcoholism or diagnosed wrongly as acute gastritis. At the same time it is to be remembered that a majority of alcoholic patients dying of cirrhosis have a normal-appearing pancreas or present only minimal evidence of pancreatic disease.

Damage to the islet mechanism was considered sufficient to cause diabetes mellitus in 18 (29 per cent), a figure which probably would have been higher if glucose tolerance tests had been done. Sixteen of these had diabetes alone, while only 2 had a history of alcoholism complicated by cirrhosis. The total of 18 seems rather high for a group in which not a single instance of steatorrhea was noted. This may be explained by the lack of routine examination of the stools for fat and also by the fact that if diabetes mellitus is diagnosed ante mortem, attention

is called to the pancreas, which is then usually examined post mortem with care. Further, if a patient with chronic pancreatitis and undiagnosed steatorrhea dies of some other condition, the pancreas may be subjected to only a cursory inspection and the lesion be missed.

Jaundice due to chronic pancreatitis has been a popular subject in medical literature. Claessen[4] mentioned a case in an alcoholic patient. It was noted in 3 patients of our study: 2 of these died following operation for the relief of jaundice and the third of a liver abscess. In the third the obstruction was chronic enough to cause biliary cirrhosis. None of the 3 cases was associated with gallstones. In the fourth instance the gallbladder contained stones but its wall was thin and no adhesions or serosal changes were noted. At operation the surgeon thought the obstruction of the common duct was due to fibrosis of the head of the pancreas. This fourth patient we observed on the ward in an attack of acute pancreatitis. At necropsy no stones were seen in the common duct. We consider this another instance of icterus due to chronic pancreatitis.

Other clinical features included an equal distribution in respect to sex, 31 females and 31 males. This is actually weighted in favor of the females because 61 per cent of all autopsies in our hospital are on males. The average age for males and females was the same, 53 years; the oldest patient was 83 and the youngest 25.

Gross Pathologic Findings

The gross appearance of the pancreas at necropsy is characteristic in severe forms of the disease, especially when perilobular fibrosis dominates. The surface is irregularly nodular. This is seen best in the lesser peritoneal cavity. Adhesions occur here frequently. Increased resistance to cutting depends on the degree of fibrosis and may call attention to the disease. Dilatation of the ducts is common and a routine dissection of the duct of Wirsung is mandatory. The duct of Santorini may be explored with a probe after the duct of Wirsung has been opened. We have seen the dilated ducts filled with thick gray fluid, with a consistency approaching that of jelly. No evidence of stricture blocking the ducts was noted in this series.

In diffuse fibrosis the gross appearance of the gland may be deceptive and diagnosis may depend on microscopic examination. Reduction in the size of the pancreas may or may not occur. This depends upon whether atrophy or fibrosis and inflammation predominate. The gland may even be above normal weight.

A variety of complications were observed in the 62 cases studied. Pseudocysts were noted in 6. Terminal acute pancreatic necrosis was

present in 16 and in 4 it was the cause of death; in the remainder it varied from a few foci to many areas of recent necrosis and hemorrhage. Some were healing and one had gone on to abscess formation. Other complications in this series included one instance of obstruction of the splenic vein and 3 of obstruction of the common duct. Biliary cirrhosis was present in 2 of the latter. We included in this study all cases with stones in the ampulla of Vater causing chronic pancreatitis, in order to evaluate the incidence of this etiologic factor. This combination was diagnosed only 4 times in the 33,500 autopsies. In 2 of these no sections of the pancreas were available, so only 2 are included in the 62 cases. Later, in a study of acute pancreatitis, we will show the low incidence of stone in the ampulla as a cause of fatal pancreatitis. Twelve (20 per cent) of this group had stones in the gallbladder without evidence of disease of the common duct. This incidence is somewhat higher than the 13 per cent observed in adults in the entire autopsy series.

Microscopic Pathologic Findings

Normal and Controls. A better understanding of the changes in chronic pancreatitis is obtained if certain details of the normal histologic structure are recalled. Although there is considerable variability, primary lobules as such rarely exceed 2.5 mm. in diameter. The majority are 1 mm. or less. Often the margins are ill defined and groups of lobules form secondary lobules up to 5 or 6 mm. in diameter. These larger masses we have noted especially near the axial center of the pancreas, but these also give the pancreas its external appearance. Occasionally, even a primary lobule seems to have a distinct separation into smaller portions. The connective tissue between the primary lobules is scanty. It may be a little more abundant between secondary lobules.

The blood supply is peculiar in one respect; in general, the vessels are dissociated from the duct system, entering the septa between lobules while the ducts enter the lobules and tend to be enveloped by them. Only rarely does one see a duct and venule or arteriole side by side. This factor is of more importance in acute pancreatitis, where thrombosis is common.

Control material was taken from individuals of all decades. In older people there may be some increase in perilobular connective tissue, fatty infiltration between the lobules, ductal epithelial hyperplasia, and atrophy. The last is of particular interest because it may be focal in character, involving one or two lobules only. In such areas, also, there may be hyperplasia of the epithelium of the ducts. These changes are similar in some respects to those in chronic pancreatitis. In some instances they accompanied arteriosclerosis of severe degree, of which

they could be considered the result. In others no etiologic factor was noted. Bosanquet[29] found some degree of pancreatic fibrosis in 10 per cent of patients over 40 years of age. Even in the aged the pancreas may be indistinguishable from that of a young adult.

Chronic Pancreatitis. Because so many of the pancreases in this group were the seat of recent acute changes, some of which were in the healing stage, an unusual opportunity to study the histogenesis of chronic pancreatitis presented itself. Although most of these lesions have been recorded in the past, we will outline them and discuss particularly the rôle of lobular necrosis. The examination of histologic preparations with a hand lens may give the pathologist the best evidence of the degree of fibrosis and lobular atrophy. The most striking changes occurred in the connective tissue. Most recent authors use the descriptive terms "interlobular" and "intralobular" or "interacinar"; these are so similar that we will replace the first with the older term "perilobular." The proliferation of connective tissue was, in every instance except one, greater in the perilobular than in the lobular compartment. In 3 cases the fibrosis was best described as diffuse and no accentuation of lobular pattern could be discerned. The degree of both perilobular and intralobular fibrosis was graded from 1 plus to 4 plus. This grading was arbitrary and often based on one histologic section in the file, but it was nevertheless an approximate indication of the incidence of the various grades of fibrosis. The perilobular increase was usually one or two grades more severe than the intralobular fibrosis. Because the degree of fibrosis might vary from one part of the pancreas to another, we combined those with 1 plus and 2 plus perilobular fibrosis into one group and those with 3 plus and 4 plus change into a second group. Those with diffuse fibrosis form a third group. Table I presents the grading and the relationship to alcoholism, cirrhosis, and diabetes mellitus.

TABLE I

Relationship Between Perilobular Pancreatic Fibrosis and the Presence of Alcoholism, Cirrhosis, and Diabetes

Perilobular fibrosis		Alcoholism	Cirrhosis	Diabetes
Grade	Number			
1+ and 2+	31	10	8	13
3+ and 4+	28	11	12	4
Diffuse	3	3	2	1
Total	62	24	22	18

The cellularity and maturation of the connective tissue varied widely with the age of the lesion. The older were densely fibrotic and relatively acellular. In the younger, connective tissue with more fibroblasts was

noted and the amount of collagen was not so striking. The perilobular connective tissue surrounded lobules of variable size; in some instances it seemed that larger lobules had been broken up into several smaller ones. Thus the distinction between perilobular and intralobular connective tissue becomes a matter of interpretation. In the 3 pancreases in which fibrosis was diffuse, no difference in severity between the intralobular and perilobular areas was noted. In 2 of these there was some tendency toward obliteration of the lobular pattern. In the third no evidence of lobules could be seen in most of the tissue (Fig. 1). The diffuse fibrosis had separated acini and surrounded islets and ducts indiscriminately. This occurred in a 52-year-old Caucasian who admitted drinking one-fifth of a gallon of whiskey daily for many years. He died of Laennec's cirrhosis. We have seen no report describing diffuse fibrosis of the pancreas of this type.

One important histologic finding related to the genesis of the disease should be emphasized. This is destruction of portions of lobules or of entire lobules during an acute attack (Fig. 2). Usually this occurred in foci involving only one or two lobules. Such lobular destruction was present, however, throughout many sections of the pancreas. The necrotic acini were often in the periphery of the lobule. Various stages of connective tissue replacement of such lobules were seen. If only the peripheral rim of acini was destroyed, the new connective tissue would simply widen the perilobular bands. Finally a large proportion of the original lobule might be replaced by connective tissue (Fig. 3). A few acini, an occasional duct, and perhaps an islet would be all that remained. Where several lobules had been destroyed (Fig. 4), larger areas of fibrous tissue occurred (Fig. 5). Connective tissue replacement might subdivide some lobules into smaller ones with great distortion of the normal pattern. Infiltration of polymorphonuclear leukocytes, hemorrhage in the acute stage, and sooner or later many lymphocytes, completed the inflammatory picture. Often hemosiderin was the telltale sign of previous attacks of acute hemorrhagic pancreatitis.

It seemed that the end result in the pancreas depended on two factors: first, the proliferation of perilobular and intralobular connective tissue, resulting in the formation of lobules of variable size, and second, lobular destruction. Whether the first could follow minimal attacks of pancreatitis without necrosis could not be proved from histologic study. Changes in the remaining acini were few. Usually dilatation was not seen. As Rich and Duff[30] pointed out, the cells spread apart easily if there was increased back pressure, allowing the escape of fluid.

Alterations in the duct system included dilatation, hyperplasia, and

squamous metaplasia. The degree of dilatation of the ducts was variable, in general being in proportion to the severity of the fibrosis. As noted under gross pathologic findings, explanation of the dilatation is not easy, as mechanical obstruction was rarely described. The possibility of its being due to chronic inflammation and contraction of fibrous tissue, as in bronchiectasis, has to be considered. The hyperplasia of the ducts included both increase in numbers and an unusual epithelial hyperplasia (Figs. 6 and 7). As pointed out by previous authors,[31] there is the possibility that the numerical increase follows lobular destruction in much the same manner that bile duct hyperplasia follows destruction of functioning elements. That the numerical and epithelial hyperplasia might lead to neoplasia is logical. Yet we have not been able to prove this relationship in any pancreas. Many carcinomatous pancreases have chronic pancreatitis distal to the obstructing carcinoma, but this does not indicate that pancreatitis came first. A few lesions designated as chronic pancreatitis in this autopsy series, when reviewed, proved to be carcinomas.

The dilatation and hyperplasia of ducts often involved the smaller radicles, including the intercalary group (Fig. 8). This, coupled with the pink-staining débris within them, we believe, is important in the formation of calculi. It is difficult to explain the failure of the ducts to empty. Possible functional or organic failure of the acini to secrete enough juice to wash out the débris may be a factor.

Vascular sclerosis (Fig. 9) usually was most severe in areas of fibrosis and destruction; the action of trypsin in destroying vessels, as noted by Rich and Duff,[30] might have led to many of the chronic changes.

The degree of destruction of islets was difficult to evaluate because there was no way of knowing from what part of the pancreas the sections had been taken. The islets in 13 of the 62 cases showed some degree of destruction or degenerative change (Fig. 10). Seven of these patients had diabetes mellitus clinically. As is seen in Table I, the most severe degrees of pancreatitis (3 plus and 4 plus) were not so often associated with diabetes mellitus, while two-fifths of those with 1 plus to 2 plus change had diabetes. The most severe type of pancreatitis (4 plus) was often seen in alcoholic patients and the correlation of alcoholism and diabetes is not very close, as only 2 of the 24 alcoholic patients had diabetes. At least, one can say that the alcoholic person may develop severe chronic pancreatitis without diabetes mellitus. As mentioned in an earlier paper,[32] the destruction of islets may proceed at a rate parallel with that of the acini, and diabetes may thus supervene before steator-

rhea. The destruction of islets may result from their incorporation in areas of lobular necrosis or from fibrosis and ischemia. One difficulty in interpretation of the islet changes is the fact that we do not know how much actual destruction is necessary in any particular person before the diabetic state is established. It seems likely that some unknown mechanism is responsible in diabetic patients who have what appears to be sufficient islet tissue at necropsy.

The genesis of pseudocysts could be seen especially well in one case. In areas of necrosis and hemorrhage the liquefaction of tissue had formed many cyst-like spaces lined with shaggy sheets of necrotic material. In many instances necrosis had involved the parenchyma, and in one portion of the circumference of a cyst, ducts could be seen which apparently opened into it. Older cysts were present also, with recent areas of necrosis and hemorrhage in their walls, indicating activity of enzymes in a cyst with an acute exacerbation. Finally, pseudocysts may remain for years. Their thick fibrotic walls may even calcify.

One motivating purpose back of this study was the possibility of finding all stages of calculus formation and/or calcification of the pancreas in such a large group of chronically diseased organs. In spite of a most careful search, we were able to demonstrate small calculi in only one duct (Fig. 11) and two microscopic areas of calcification in fibrous tissue. It was impossible to decide if the latter represented calcification in diseased ducts or acini, or perhaps calcification in the interstitial tissue. From our study in this series and in a large experience with acute pancreatitis, we believe it is most unusual for calcification to occur primarily in the interstitial connective tissue of the pancreas or to persist in areas of fat necrosis. The reasons for this will be discussed in detail in Part II.

Discussion

In the study of this material, certain clinical and pathogenetic phases of chronic pancreatitis are manifest. First is its incidence in a large general hospital. No comparable statistics were noted in the literature. Our finding of 62 examples in 33,500 autopsies, or 0.18 per cent, probably explains the low "index of suspicion" of the clinicians and the difficulty in diagnosis. The paucity of symptoms and findings of chronic pancreatitis may be partially due to lack of interrogation and routine use of such laboratory procedures as serum amylase and stool analysis for fat. In this group, selected because of

unquestionable evidence of pancreatic damage, we were surprised to find so few in whom there was a history of acute attacks of pancreatitis such as described by Comfort *et al.*[1] Abdominal symptoms that might be related to the pancreas were noted in only 4 cases. However, the fact that acute pancreatitis was present at necropsy in 16 of the patients with chronic pancreatitis is strong evidence that the chronic changes were due to previous acute attacks.

The correlation noted in this series between the pancreatic lesion and alcoholism, with or without cirrhosis (24 cases), is similar to that found by others.[23-27] The occurrence of pancreatitis in alcoholic patients with fatty cirrhotic livers we believe, has roughly paralleled the great increase of alcoholic cirrhosis noted in the Los Angeles County Hospital in the past 14 years. Evans and Gray,[33] in 1938, noted a rise from 0.65 to 1.84 per cent of all autopsies following the repeal of prohibition. From 1939 to 1946 it rose to 5.9 per cent of autopsies in subjects over 9 years of age.[34]

In this series the chronic alcoholic patients certainly had the highest incidence (10 of 24) of acute pancreatitis at necropsy. Once the pancreas has been the seat of an acute attack, the likelihood of further attacks seems enhanced, providing the same etiologic factors continue to operate. Paxton and Payne,[28] in their report on pancreatitis from this hospital, found that 61 per cent of their patients had a history indicating similar previous attacks. From studying the clinical course and seeing the lesions at necropsy one gets the idea that repeated episodes of subclinical character commonly occur. These are probably due to escape of pancreatic juice and would explain the stubborn chronicity noted clinically in relapsing pancreatitis. We have been impressed by the lack of evidence of pyogenic complications such as abscesses in both acute and chronic pancreatitis. All stages of the disease appear to be explainable by the enzymatic theory. Acute pancreatitis may be the terminal event also in a cirrhotic patient who is not consuming alcohol at the time. The mechanism of the production of pancreatitis by alcohol is not known but its relationship has been shown repeatedly.

That the fatty liver might be related to acute pancreatitis in some unknown way is suggested by the experiments of Groen.[35] He fed 9 dogs fat bacon exclusively. Death occurred, often suddenly, in 5 dogs within 5 to 7 months. Severe fatty infiltration of the liver was noted in all. Four of the 5 animals had acute pancreatic necrosis. Microscopically, the pancreatic ducts were blocked by an unidentified material which could have caused necrosis by obstruction.

The fundamental histologic change in chronic pancreatitis is fibrosis. This, in turn, is characterized by its great variability as to degree and results. It varies from one part of the pancreas to another and from perilobular to intralobular compartments. The quantity of acinar and islet atrophy is often unpredictable from a survey of the fibrous change. Duct changes likewise may not correspond to the degree of fibrosis. That fibrosis is due to one or more attacks of acute pancreatitis is certainly true in many instances, but in those patients without symptoms a definite etiologic factor cannot be assigned. Minimal or subclinical attacks of upper abdominal pain indicative of pancreatitis but forgotten by the patient are a possibility not to be dismissed.

The pattern of the fibrous change probably depends upon the severity of the acute attacks; edematous pancreatitis may result in fibrosis predominating in the perilobular spaces. In more severe attacks, as we have shown, lobular necrosis and replacement with fibrous tissue causes more extensive scarring and often a nodular pancreas. With repeated attacks, more and more acinar and islet tissue would be destroyed, finally resulting in a fibrosed, atrophic organ with deficiency in external and/or internal secretion. Strangely enough, in this series diabetes was the most common complication. Steatorrhea could have been overlooked because stools are not examined routinely for fat as is the urine for sugar.

One difficult problem that arose during this study was that of establishing histologic criteria to distinguish chronic pancreatitis, with extensive islet destruction and diabetes, from the atrophic gland containing hyalinized and fibrosed islets, seen frequently in elderly diabetic patients. Opie[3] described an interacinar form of chronic pancreatitis with destruction of islets in patients with diabetes mellitus. He considered that this was probably the same disease as that previously described as atrophy of the pancreas. It seems doubtful if such a change should be classified as a form of chronic pancreatitis. Although examples of this change were noted in the autopsy material, they were not included in the final study. Histologic evidence of true chronic pancreatitis includes dilatation of ducts and hyperplasia, round cell infiltration and lobular destruction with replacement fibrosis. Yet in healed pancreatitis of many years' duration an atrophic gland remains which on histologic examination alone presents a difficult problem in interpretation. This was shown by one of our cases, a white woman, 58 years old, who died in uremia due to pyelonephritis and nephrosclerosis in April, 1938. She had had a laparotomy for

acute pancreatitis in 1903. Diabetes mellitus was diagnosed in 1923. Upper abdominal pain and tenderness had been described on admittance to the hospital in 1934. At necropsy a large pseudocyst, 17 cm. in diameter, involved the body and tail of the pancreas. Its wall was calcified. Yet, on microscopic examination of the remaining pancreatic tissue, a diagnosis of chronic pancreatitis could be made only with difficulty. Only atrophy and fibrosis were seen. This case emphasizes the importance of the clinical story. Those patients in whom there is no gross or microscopic evidence of past acute episodes with resultant chronic changes should at least be put in a questionable diagnostic category.

The changes in the duct system are of interest. Dilatation may be severe, and when accompanied by sufficient destruction or functional failure of acini the ducts fail to empty and the inspissated pink-staining material seen microscopically accumulates in many of the branches. In this débris, calcium salts may be precipitated, as was noted once. Hyperplasia of ducts and their epithelium is probably reparative and the possibility of tumor formation exists.

Though chronic pancreatitis may become manifest by all the symptoms and signs that have been so well described, it is most puzzling that severe morphologic changes can occur in the organ and the patient remain symptomless.

Because of the incidence of acute pancreatitis, especially that associated with alcoholism, in such an institution as the Los Angeles County Hospital, it seems inevitable that chronic pancreatitis will in the future occupy a more significant position in clinical diagnosis than it has in the past.

Summary and Conclusions

Sixty-two instances (0.18 per cent) of chronic pancreatitis were found in 33,500 autopsies.

Twenty-four of the 62, or 38.7 per cent, gave a history of excessive use of alcohol. Nineteen of the alcoholic patients also had portal cirrhosis.

Eighteen, or 29 per cent, were diabetic. Diabetes was more often associated with moderate degrees of pancreatic fibrosis and only twice was it seen in alcoholic patients.

The difficulty in diagnosis of chronic pancreatitis is emphasized by the fact that none was recognized clinically. A history of abdominal pain typical of pancreatitis was elicited in only 4.

In contrast to the symptomless course, at necropsy 16 had evidence of acute pancreatitis; in 4 it was the cause of death.

The distribution of lobular necrosis is important in determining the pattern of the resulting fibrosis.

Perilobular fibrosis is the predominating change. Diffuse fibrosis of a peculiar type was noted once.

Early deposition of microcalculi in the ducts was seen once.

Biliary calculi impacted in the ampulla of Vater as a cause of chronic pancreatitis occurred twice.

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DESCRIPTION OF PLATES

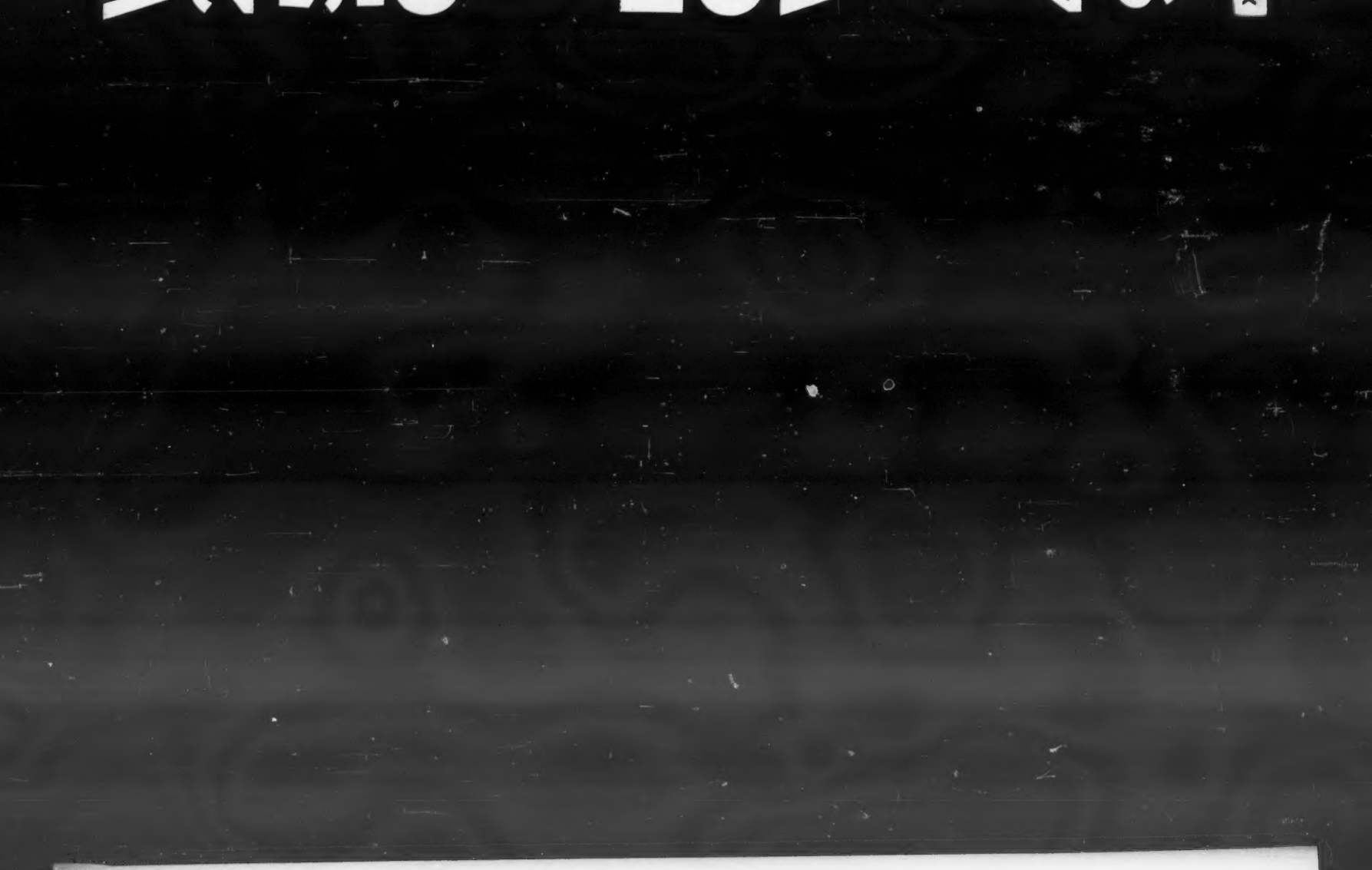
All illustrations were prepared from sections stained with hematoxylin and eosin.

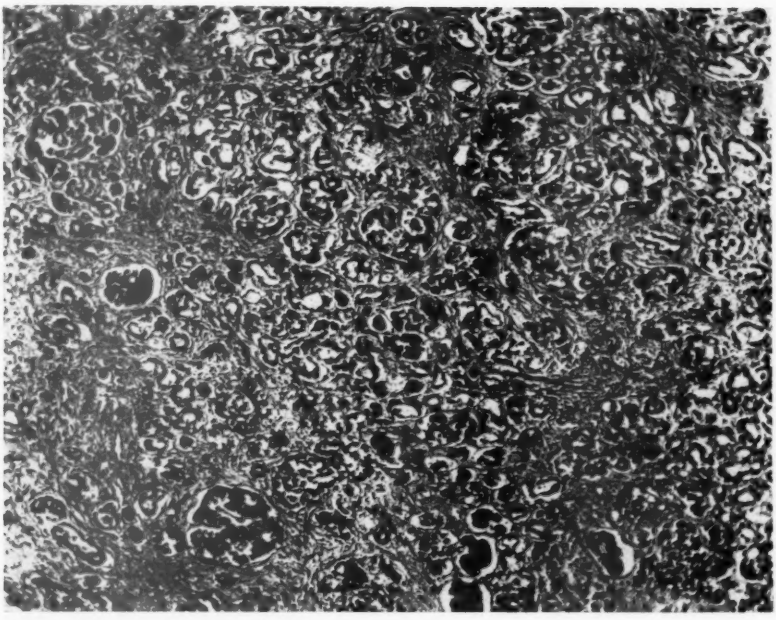
PLATE 191

FIG. 1. Diffuse fibrosis of the pancreas with obliteration of lobular architecture. × 70.

FIG. 2. Early necrosis of peripheral portion of a lobule. The perilobular fibrosis indicates chronicity. × 63.

FIG. 3. The connective tissue replacement of portions of lobules represents the end stage of partial lobular necrosis shown in Figure 2. × 63.





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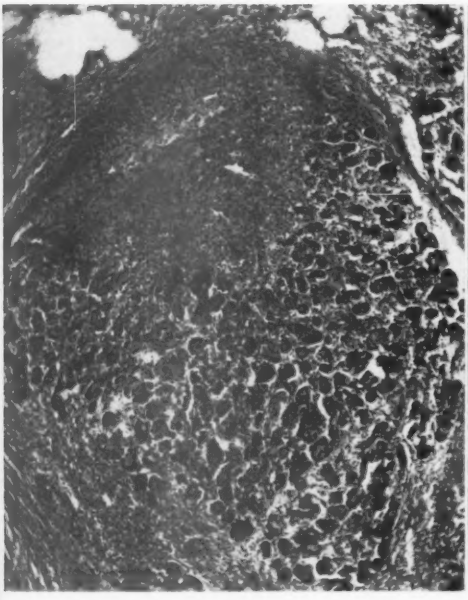

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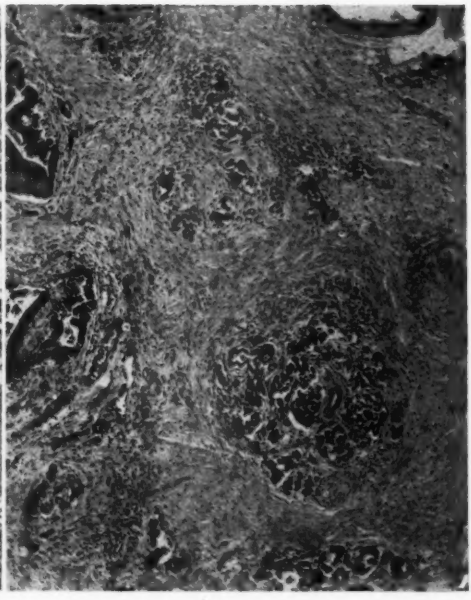

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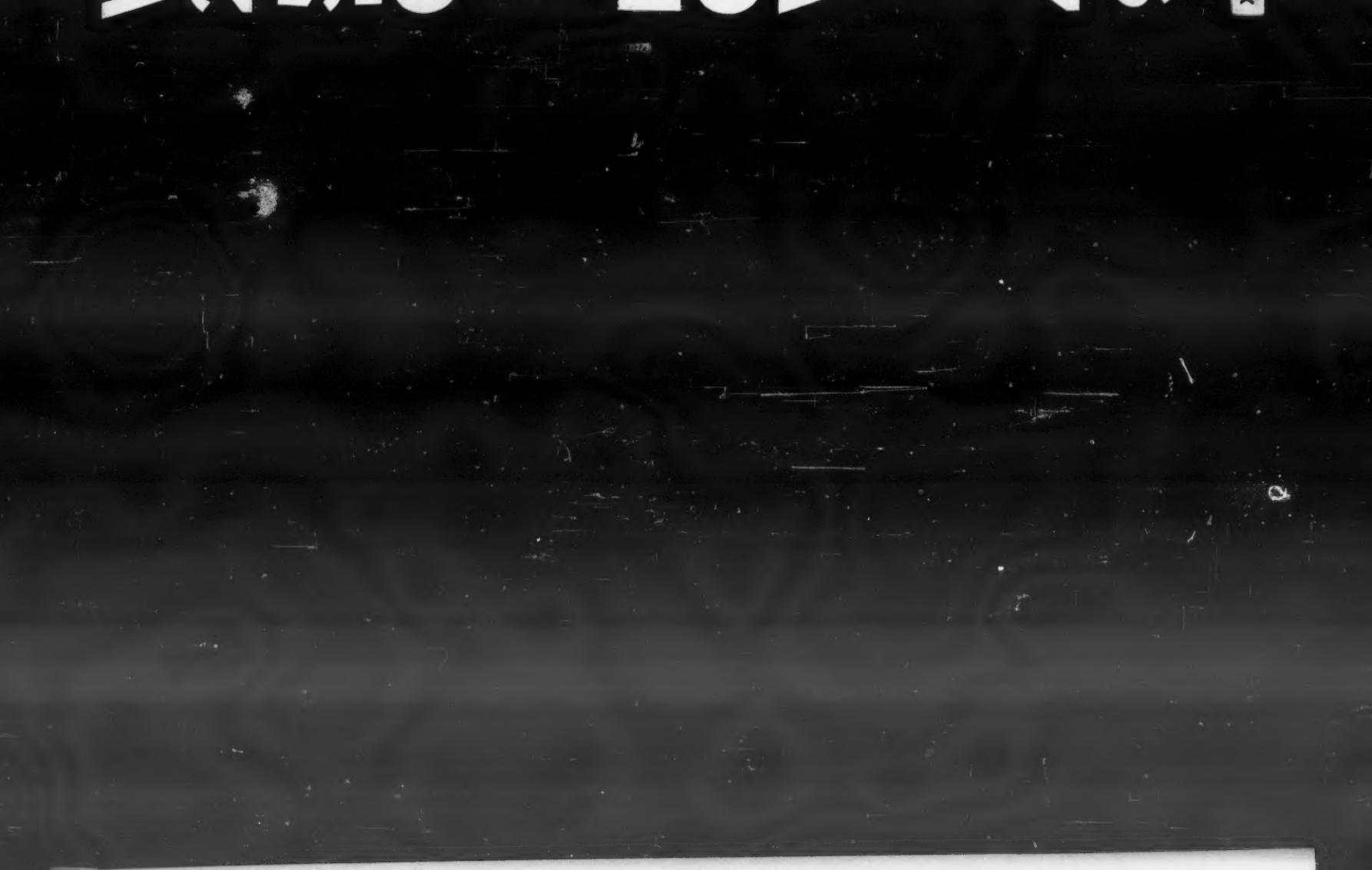
PLATE 192

FIG. 4. Lobular necrosis involving several lobules. Connective tissue proliferation and round cells at margin of necrotic area indicate the beginning of healing. × 68.

FIG. 5. Extensive fibrosis following complete lobular necrosis, such as seen in Figure 4. × 68.

FIG. 6. Dilated duct showing a portion of its epithelium undergoing hyperplasia. Secondary duct lined with similar epithelium. × 37.

FIG. 7. Higher magnification of junction of normal and hyperplastic epithelium shown in Figure 6. × 220.



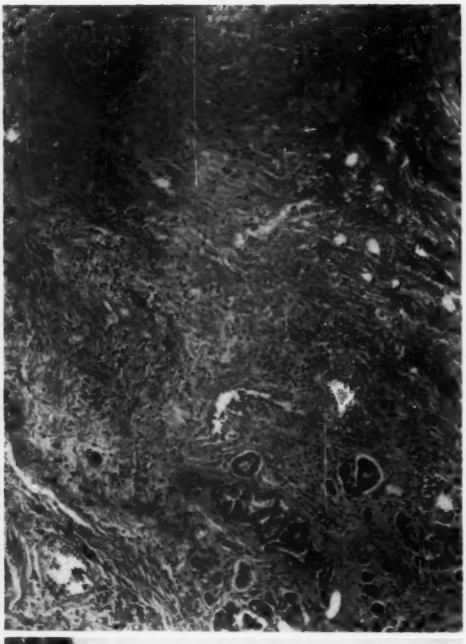


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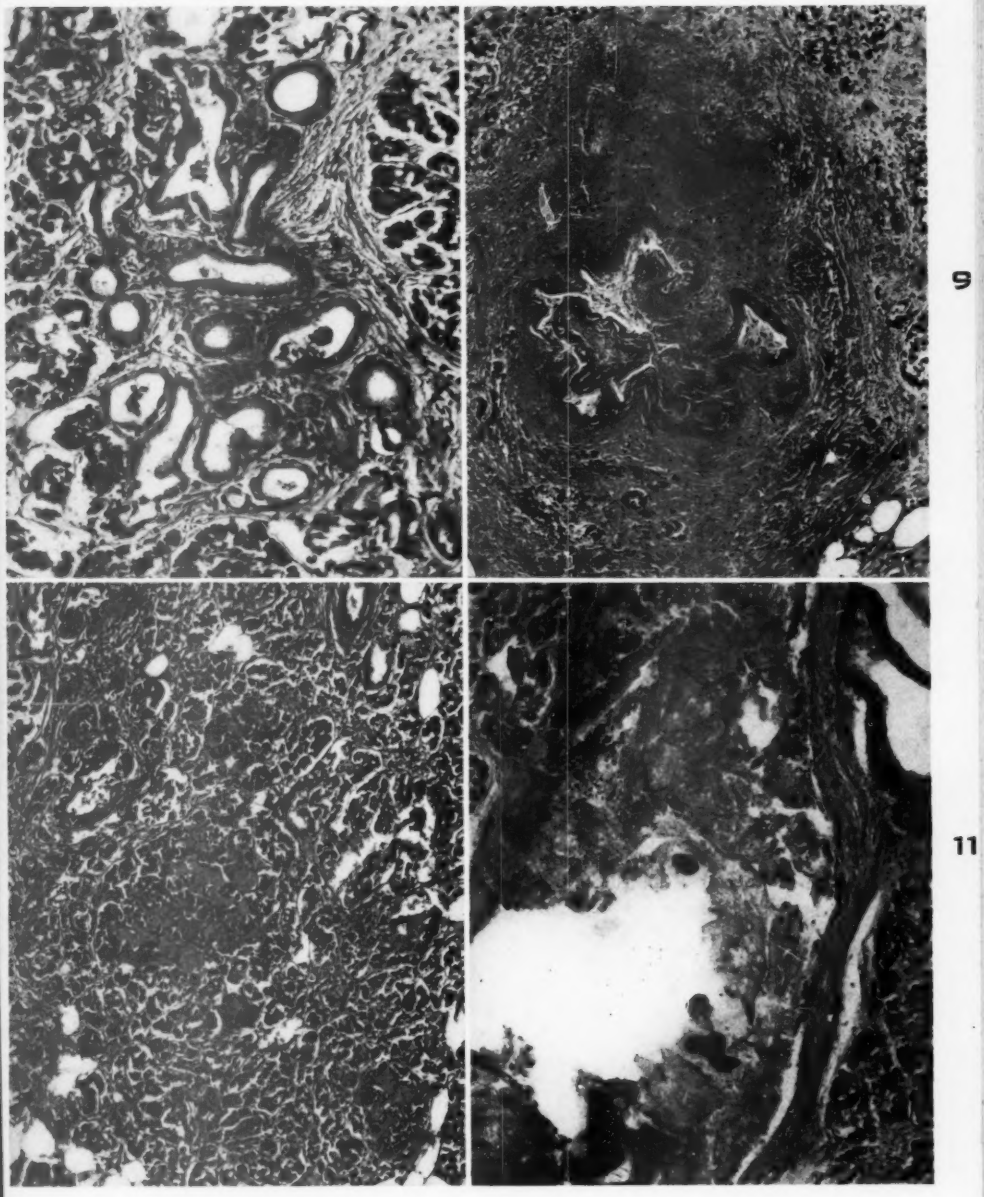
PLATE 193

FIG. 8. Dilatation and hyperplasia of ducts within a lobule. × 132.

FIG. 9. Hyalinized remains of blood vessel in chronic pancreatitis. × 70.

FIG. 10. Hyaline changes in islets of Langerhans. Chronic pancreatitis. History of chronic alcoholism. Diabetes mellitus not proved. × 66.

FIG. 11. Small calculi precipitated in pink-staining débris of a dilated pancreatic duct. × 79.



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